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Perspective

PERSPECTIVE

Can the personalized medicine approach contribute in controlling tuberculosis in general and India in particular?

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Abstract

Poor drug compliance and drug-resistant *Mycobacterium tuberculosis* are the two principal obstacles in controlling tuberculosis (TB) in endemic regions including India, which has contributed the most to global TB burden. We argue here that a personalized medicine approach, to start with the *N*-acetyl transferase-2–isoniazid (NAT2–INH) model, could be a step forward in dealing with both these limitations in controlling TB in India.

Key words: tuberculosis; personalized medicine; isoniazid; *N*-acetyl transferase-2; India

India contributed the most to the global tuberculosis burden

Tuberculosis (TB) is an age-old disease of humankind and a leading life-threatening infectious disease caused by a mycobacterial pathogen, *Mycobacterium tuberculosis*.[1] TB is one of the top 10 causes of death globally and the primary reason of mortality from a sole infectious agent. The pathogen *M. tuberculosis* typically affects the lungs, called pulmonary TB, but the bacterium also can affect other parts of the human body, known as extrapulmonary TB. According to a global TB report in 2019, about 10 million people got infected with TB worldwide with an average of 130 per 100 000 populations.[2] While the Southeast-Asian countries contributed the most (44%), India ranks the highest among all endemic countries (27%) with about 2.7 million cases in 2018 with an average of 199 per 100 000 population and ranks second in terms of TB-related mortalities globally.[2] In 2018, India reached the target of achieving notification very close to the estimation, which was a 16% increase on the preceding year.[3] The burden of TB is not equal in all the Indian states; the state of Uttar Pradesh, with 17% of the Indian population, contributes to 20% cases with 187 cases per 100 000 population. Very similarly, the Indian indigenous populations (tribes) were found to be highly burdened by TB with about 703 cases per 100 000 population[4] – about three times higher than the Indian average and more than five times higher than the global average. Moreover, in a particularly vulnerable tribal group, such as one named the "Saharia" and residing in the central Indian states of Madhya Pradesh, the prevalence can go up to 3294 per 100 000 population.[5] Further, about one-quarter of the global burden of multidrug-resistant tuberculosis (MDR-TB) comes from

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India and also poor anti-TB drug compliance.[2] This justifies a great disparity on the prevalence of TB in India based on the standard of living and the type of population; meaning one single strategy for TB control might not work. Such disproportional prevalence of TB across India justifies genetic variations in both the pathogen *M. tuberculosis* and also the human susceptibility to TB.

Why personalized medicine for TB?

As a general understanding, the human genome behaves differently to susceptibility to different diseases, which are unique in different human populations.[6] Advancement in biomedical research and usage of modern biological techniques have revolutionized the medical sciences in recent years, which has made the task of capturing the net genetic variations in the population easier than ever. Knowledge on the association of human genes to different diseases and therapy based on individual genetic makeup (personalized medicine) has therefore begun to develop and is being used for different diseases. As per the present protocol, chemotherapy is the only way to treat TB. However, it has been seen that not every individual is declared completely cured at the end of the defined treatment regimen, justifying individual genetic variation in TB patients in responding to drugs (e.g. effectiveness of drug metabolism).[7] Also, variation in the infected mycobacterium strain in terms of drug sensitivity can also define the effectiveness of treatment [e.g. infection of drug-resistant *M. tuberculosis*, defined as multiple-drug resistant (MDR) or extremely drug resistant (XDR)]. Both these factors (effectiveness of individual drug metabolizing capacity in human and infection of drug-resistant mycobacterium) define success of TB treatment, and therefore contribute to success in the elimination program.

Human genetic factors play a major role in mitigating these two aspects to a greater extent as several genes in humans involved in defining susceptibility to mycobacterial disease have been identified. For example, mutation in a gene coding the chemokine (C-C motif) ligand-2 (CCL2), essential for the recruitment of monocytes and T-cells, may enhance the risk of developing TB.[8] Similarly, a polymorphism of the human tumor necrosis factor gene was found to be associated with a weakened response to TB treatment.[9] Further, genome-wide association study has identified novel loci that might influence the risk of developing active TB among latently infected individuals.[10] Moreover, it is known that anti-TB drugs cause hepatotoxicity, and production and elimination of the poisonous metabolites depend on the actions of certain human enzymes, such as *N*-acetyl transferase-2, cytochrome P450 oxidase, glutathione S-transferase, interlukin-12, interferon-gamma, etc. Studies have shown that mutations in these genes could alter the activities of enzymes and increase/decrease the risk of hepatotoxicity, and also may individually or together add to the prognosis of TB.[11] Since mutations in different genes vary according to human ancestry and adaptation to different environmental conditions, consideration of such polymorphic mutations is essential while tweaking the chemotherapy of TB based on personalized genetic information. Any medicine thus prepared based on individual genetic variation will be far more effective than conventional medicine, with less hepatotoxicity and unwanted drug toxicity.

The INH-NAT2 model: beginning of personalized medicine in TB

As is widely known, much of the failure to curb TB is due to (i) drug-resistant TB and (ii) poor drug compliance due to adverse drug reactions. Incidentally, both effectiveness in drug metabolization and evolution of type of *M. tuberculosis* in term of drug sensitivity seem to be grossly dependent on the genetic makeup of the patient for metabolization of the major first-line antitubercular drug, isoniazid (INH). As is already known, INH is metabolized internally by a non-inducible hepatic and intestinal enzyme called *N*-acetyl transferase-2 (NAT2).[12] In addition to INH, NAT2 metabolizes a wide variety of therapeutic agents including dapsone (leprosy and malaria), sulfadoxine (malaria), etc.[13] For effective utilization of INH in human through metabolism, proper biotransformation of INH is needed, which happens through NAT2 in three different steps: (i) deactivation [formation of acetylisoniazid (AcINH)], (ii) bioactivation [(formation of acetylehydrazine (AcHz)], and (iii) detoxification [formation of diacetylehydrazine (DiAcHz)].[12] Incidentally, the *NAT2* gene is highly polymorphic; on the basis of single nucleotide polymorphisms present in the second exon, different alleles that are assigned to two broad metabolization phenotypes (slow or fast) have been found in different populations with global interethnic variations.[14] Accordingly, it has been determined that a patient with a slow acetylation phenotype can metabolize INH slower than the fast phenotype. For the patient with a fast acetylation phenotype, INH reaches the target site quickly and is cleared from the body much faster and more efficiently; whereas activities of the slow ones are grossly compromised. Experimental proof has come from a study involving 130 patients from Poland, where NAT2 slow acetylators had 2–7-fold higher INH concentrations at 3 and 6 h after drug administration than the fast acetylators.[15] Therefore, a patient with the slow *NAT2* acetylation phenotype unnecessarily accumulates INH, which not only can cause toxicity, thereby causing side effects, but also the availability of the drug in low concentrations can create an ambient environment for the mycobacterium to evolve drug resistance. This makes the acetylation phenotype of a TB patient important for effective and efficient treatment in th first place, and for TB public health as well. Furthermore, it has been shown that the *NAT2* genotype-guided medicating stratification of isoniazid bears tremendous potential,[16] which

supports use of the *NAT2* genotype to monitor INH dosing strategies in the management and prevention of TB.[17]

Possible strategies of *NAT2*-INH-based personalized medicine

Considering INH is one of the first-line treatments for TB and that a clear association exists between different genotypes and metabolism of this drug in humans, the first-step of personalized medicine should be taken with genetic profiling at *NAT2* and accordingly the tweaking of INH. The following strategies can be considered in this direction. First, (i) a TB patient could be classified for acetylation phenotype based on the allele of the *NAT2* gene, and (ii) the doses of INH with appropriate concentration and frequency based on the possession of acetylation phenotype could be determined and administered. In this way, a database of the *NAT2* genotypes will be prepared in India, which can also be used for developing similar precision medicine approaches for other diseases (see above). For example, while keeping the daily dose per kilo body weight to the same level for both the acetylation phenotypes, a patient possessing the slow acetylation phenotype (as determined by the NAT2 genotype) can get INH in a lower concentrations than the currently determined dose but with frequent repeats, whereas a patient possessing the fast acetylation phenotype can get the effective concentration with currently determined repeats.[18] To this extent, such an approach should begin from India. This is because, (i) India shoulders the most burden of the TB and MDR-TB cases around the globe,[2] and (ii) computer modeling studies indicated 85% India's TB cases to be MDR by the year 2032 due to primary transmission.[19] Also, (iii) Indians possess a high diversity of *NAT2* genotypes with many novel acetylation phenotypes that are otherwise absent in other countries.[14] Therefore, a personalized treatment approach, as that described, could prove as a game-changer for India's ambitious plan of TB-free India by 2025. Since drug-resistant TB is suggested to challenge TB-free India plan by 2025,[20] with no current vaccine available for prevention of TB infection, to preclude evolution and spread of drug-resistant TB, a personalized medicine approach can prove to be an advantage to control TB to a large extent. This would further lessen discomfort to patients due to unwanted drug toxicity (primary cause of poor treatment compliance), and provide effective treatment by fast mycobacterial clearance, thereby achieving the status of 'TB-free India' by 2025 and contributing to global TB elimination by 2030.

Conclusions and future prospects

The concept of precision medicine in TB has been a subject of discussion in recent times. Accordingly, new therapeutic guidelines are recommending personalized treatment based on drug-susceptibility testing (DST) results.[21] Further, DST must ideally be coupled with information about antibiotic pharmacokinetics (PK) and pharmacodynamics (PD). To this direction, the pharmacology committee of the Global Tuberculosis Network is promoting Therapeutic Drug Monitoring (TDM).[22] With the TDM technique, it has become fairly easy to dose anti-TB drugs, to ensure the precise dose, minimizing adverse events and maximizing regimen efficacy. A randomized controlled trial to compare TDM with standard of care to show the profits of precision dosing should be the next step.[23]

Considering the fact that genotype-based dose determination can be easily possible for TB in the *NAT2*-INH system, the prospects of precision medicine in TB look quite bright. Since the evolution of MDR *M. tuberculosis* resistant to rifampicin and isoniazid is a cause of great concern,[24] personalizing treatment could help in preventing development of MDR-TB. Different host genetic polymorphisms associated with a higher risk of adverse reactions could lead to the fine-tuning TB treatment and decrease adverse drug reactions. However, to achieve this dream, concerted efforts from professionals from multidisciplinary specialisms, such as immunologists, infectious disease specialists, microbiologists, molecular biologists, nurses, occupational therapists, pharmacists, pharmacologists, social workers, etc., would be needed.[25] For this, strong political, social, and scientific commitments are necessary, by which the two major hindrances of TB control, namely poor compliance of anti-TB drugs due to adverse drug reactions and evolution and spread of drug-resistant *M. tuberculosis* in a country contributing the highest burden of TB on the globe (India), can be mitigated.

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Conflict of interest

None declared.

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