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OPTIMIZATION OF 6-MERCAPTOPURINE THERAPY IN INDIANS-SPECIFIC ADAPTATION OF GLOBAL PHARMACOGENOMICS GUIDELINE

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ABSTRACT

Pharmacogenomics is the study about individual's genetic makeup influences their response to medications, including drug efficacy, toxicity, and the likelihood of beneficial or adverse effects. The primary objective of pharmacogenomics is to optimize drug selection, dosing and combination therapies according to a patient's genetic profile. Consequently, modern healthcare is progressively transitioning from a traditional "one-size-fits-all" approach toward individualized treatment strategies that emphasize delivering the right drug, at the right dose, at the right time, and in the right manner.

KEYWORDS: Pharmacogenomics, Personalized medicine, Drug efficacy, Genetic profile.

Acute lymphoblastic leukaemia (ALL) is a cancer in which immature lymphoid cells (a type of white blood cell) multiply uncontrollably. These cells are unable to mature properly and accumulate in the bone marrow, blood, and other parts of the body, affecting normal blood cell production. The male to female ratio is about 1:2:1.[1,2] It often develops in young children's, with the highest occurrence between 2 to 5 years of age. Although many studies have explored the causes of this common childhood cancer, the preventable risk factors remain unclear.[3,4,5] For the treatment of acute lymphoblastic leukaemia (ALL), thiopurine drugs such as mercaptopurine (6-MP) are commonly used as a key component of maintenance therapy.[6]

PREVALENCE OF TPMT AND NUDT15 POLYMORPHISM

Thiopurine drugs such as 6-mercaptopurine play a crucial role in the maintenance therapy of pediatric acute lymphoblastic leukaemia; however, their clinical use is often limited by severe myelosuppression in genetically

susceptible individuals. Variants in NUDT15 and TPMT have been identified as key pharmacogenetic determinant's influencing thiopurine metabolism, particularly in Asian populations. In line with recommendation from a clinical pharmacogenetics Implementation Consortium **(CPIC)**, pre-emptive genotyping can significantly improve treatment, safety and efficacy. A study by GT Joseph et al. successfully developed and validated a rapid, cost-effective tetra primer ARMS-PCR assay for simultaneous detection of **NUDT15 c.415>T and TPMT 3C** variants. The assay demonstrated high diagnostic accuracy and strong concordance with Sanger sequencing. Importantly, the higher prevalence of NUDT15 variants and their significant association with reduced 6-mercaptopurine dose intensity highlights the clinical relevance of pharmacogenetic testing in Indian population. Given its affordability and minimal infrastructure requirements, this method offers a practical solution for integrating genotype guided dosing into routine clinical practice. Overall, this approach supports the broader implementation of pharmacogenomics in resource- limited settings, enabling safer and more personalized leukaemia treatment.[7,8,9,10]

The study by Aswin Anand Pai et al. was conducted in an Indian population of patients with acute lymphoblastic leukaemia undergoing maintenance therapy with 6-mercaptopurine. The findings demonstrated that the **NUDT15 c.415>T** variants is a major predictor of Thiopurine-induced myelotoxicity in this population, whereas TPMT variants were relatively less frequent. These results support the implementation of CPIC -recommended pharmacogenetic testing to optimize Thiopurine dosing and improve treatment safety in Indian patients.[11] Acute lymphoblastic leukaemia (ALL) treatment involves Thiopurines such as 6-mercaptopurine, whose metabolism is strongly influenced by genetic polymorphisms. The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides guidelines for dose adjustment based on variants in genes such as TPMT and NUDT15.

Significant population-based differences are observed between Indian and Europe. In European populations, TPMT variants are the primary determinants of thiopurine toxicity, with a frequency of approximately 2-7%. In contrast, Indian and Asian populations exhibit a much higher prevalence of NUDT15 variants (10-20%), while TPMT variants remain relatively rare (~2-3%). This indicates that although CPIC guidelines are universally applicable, their clinical implementation must be tailored to population-specific genetic profiles.[12]

INDIANS-SPECIFIC ADAPTATION OF GLOBAL PHARMACOGENOMICS GUIDELINES

Indian studies consistently demonstrate that NUDT15 polymorphism are strongly associated with severe myelosuppression during 6-mercaptopurine therapy. Pai et al. (2021) reported that NUDT15 variants are significantly associated with increased toxicity, making it the most relevant pharmacogenetic marker in Indian ALL patients. Similarly, Bhatia et al. (2025) highlighted that genotype-guided dosing based in CPIC recommendations significantly reduces adverse drug reactions.

In contrast, European studies emphasize TPMT genotyping as the primary strategy for dose adjustment. Relling et al. (2019), in the CPIC guideline update, demonstrated that TPMT-guided dosing reduces toxicity without compromising therapeutic efficacy. However, even in Europe, recent studies suggest that combined TPMT and NUDT15 testing provides better prediction of toxicity. Despite strong evidence supporting pharmacogenomic-guided therapy, implementation in India remains limited.

Major barriers include lack of infrastructure, high cost of genetic testing, and absence of standardized national guidelines integrating CPIC recommendations. Additionally, several Indian studies report thiopurine toxicity in patients

without known TPMT or NUDT15 variants, suggesting the involvement of other genes such as ITPA and MRP4, which require further investigation and CRIM1 has been reported as a gene associated with haematological toxicity induced by 6-mercaptopurine (6-MP). However, evidence from the studies is limited due to relatively small sample sizes, restricting genome-wide significance, along with insufficient representation of diverse ethnic populations. Therefore, further studies are necessary to better understand the role of CRIM1 in the metabolism of 6-MP.[13]

CHALLENGES AND FUTURE SCOPE OF PHARMACOGENOMICS IN ALL(INDIA)

In India, many studies on acute lymphoblastic leukaemia (ALL) are done with small number of patients, like around 61 cases, and mostly in a single hospital. Because of this, the results may not represent the whole Indian population. Also, most studies focus only on a few genetic variants like NUDT15 and TPMT, while other important genes are not studied much. Indian has high genetic diversity, but many studies do not include patients from different regions.

Another issue is that studies mainly look at short-term outcomes like drug toxicity and dose changes. They do not focus much on long-term outcomes like survival and relapse. Even though some genetic tests are accurate, they use methods like Sanger sequencing, which may not easily available or affordable in all hospitals. Also, these studies do not clearly show how these tests can be used in daily clinical practice.

In additional, different hospitals use different treatment methods and testing techniques. This makes it difficult to compare results and apply them in real-time treatment.

In contrast, in Europe, studies are done in multiple centres with many patients. They follow standard protocols and have better facilities. This helps them produce more reliable results and easily apply pharmacogenomic guidelines like those from the clinical pharmacogenetics implementation consortium in patient care.

Another critical challenge is the variability in study design and sample size across Indian research, limiting the generalizability of findings. In contrast, European data are often derived from large, multicentre trials, allowing more robust clinical application.

- To improve this in India, more large-scale and multi-centre studies are needed.
- Standard treatment and testing methods should be followed.
- Low-cost and easy genetic testing should be developed.

CONCLUSION

Overall, while CPIC guidelines provide a strong framework for precision medicines in ALL, their effectiveness in India depends on addressing populations-specific genetic variability and healthcare system limitations.

SUMMARY

Pharmacogenomics plays a crucial role in optimizing treatment outcomes in acute lymphoblastic leukaemia. The application of CPIC guidelines has significantly improved the safety and efficacy of Thiopurine therapy in genetically variant patients. However, marked differences exist between Indian and European populations in term of genetic variant distribution.

In Europe, TPMT polymorphism are the primary determinants of thiopurine toxicity, whereas in India, NUDT15 variants are more prevalence and clinically significant. This highlights the need for population-specific adaptation of global pharmacogenomics guidelines.

The major challenges in India include limited access to genetic testing, lack of awareness, insufficient infrastructure, and absence of large-scale studies. Addressing these challenges through cost-effective testing methods, incorporation of pharmacogenomics into national treatment protocols, and expanded research on additional genetic markers is essential.

Further efforts should focus on integrating CPIC guidelines into routine clinical practice in India, promoting large multicentre studies, and developing affordable genotyping strategies to enable personalized medicine in ALL treatment.

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