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Precision Medicine in Children: a Review of the Recent Literature

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Precision medicine, also referred to as personalized medicine, incorporates the patient's individual characteristics into treatment, rather than relying on population means. Over the past several years, it has become a significant focus for research. Developments in pharmacogenomics, the study of genomic variations that influence response to drugs, has accounted for much of the recent work in this area.[1,2] As of November 2016, the prescribing information for more than 150 drugs included guidance on using pharmacogenomics information in drug selection or dosing.[3] Understanding and incorporating genomic variation, however, is just one component of providing precision medicine. Age, gender, environment, and comorbidities are only a few of the potential factors to be considered in providing personalized pharmacotherapy.

Research in pediatric precision medicine, including pharmacogenomics, is growing at a rapid rate. A 2015 review of the Food and Drug Administration's pharmacogenomics biomarker labeling data identified 38 drugs with information pertinent to use of the drug in pediatric patients.[4] The authors also identified 137 pediatric pharmacogenomic studies listed on Clinicaltrials.gov. Information generated from studies in adults often can be of value in treating children, such as the identification of the correlation of human leukocyte antigen B variant allele HLA-B*1502 and carbamazepine-induced Stevens Johnson Syndrome or toxic epidermal necrolysis and the role of thiopurine methyltransferase polymorphisms in the development of thiopurine-induced bone marrow suppression.[5-7] The following studies represent a sample of the recent literature in this new field.

Asthma

The use of precision medicine in the treatment of pediatric asthma is the topic of a recent review by Pijnenburg and Szefler.[8] The authors discuss the differences and potential interface between personalized and stratified treatment, the latter representing the traditional grouping of children with asthma into subpopulations by patient characteristics (e.g., obesity) or response to a particular therapy. They address the challenges in predicting treatment response and the limitations of current tools such as pulmonary function testing to guide therapy. The authors suggest that response to the mainstays of treatment, inhaled corticosteroids, beta-2 agonists, and leukotriene receptor antagonists, is, in part, genetically determined and that research should be focused on identification of patient phenotypes most likely to benefit from their use. The authors also include a discussion of biomarkers such as fraction of exhaled nitric oxide (FeNO), sputum eosinophil count, and exhaled breath or exhaled breath condensate in guiding drug selection or dose titration. The authors conclude by highlighting the need to use these new technologies in concert with traditional individualized patient care techniques, such as family-centered medication education, to maximize treatment adherence.

Attention Deficit Hyperactivity Disorder

In a new review of the treatment of attention deficit hyperactivity disorder (ADHD), Connolly and colleagues discuss both current options and potential avenues for new treatment advances.[9] This review poses several interesting predictions for future pharmacogenomics research, including the potential for new therapies based on research showing that patients with ADHD have a significantly higher frequency of recurring copy number variations in GRM genes encoding for

metabotropic glutamate receptors (mGluRs) than those without ADHD.

A recent paper by de Leon in the *Journal of the American Academy of Child and Adolescent Psychiatry* described the difficulties in assessing the impact of cytochrome P450 2D6 genotype on metabolisms of atomoxetine.[10] The author reviews the current FDA guidelines for pharmacogenetic testing to determine cytochrome P450 2D6 function, as well as the results of studies of amoxetine kinetics in CYP2D6 poor and ultra (rapid) metabolizers. In spite of a 10-fold increase in plasma concentrations in patients who are CYP2D6 poor metabolizers compared to extensive (normal) metabolizers, there appears to be little effect on therapeutic response or toxicity. Ultrarapid metabolizers, however, are at risk for a subtherapeutic response to standard dosing. Higher doses may be appropriate, but to date there have been no specific dosing recommendations published to guide therapy and no consistent approach to using this information in clinical practice.

Autism

A paper from Bowers and colleagues at Cincinnati Children's Hospital summarizes studies conducted to date on pharmacogenomic studies of selective serotonin reuptake inhibitors and atypical antipsychotics in patients with autism.[11] The article includes a detailed table of these studies, including the genetic variants identified and their effect on treatment. The authors also describe potential new therapies such as the NMDA receptor glycine-site partial agonist GYLX-13 that may ameliorate some core symptoms of autism.

Cardiac Transplantation

Van Driest and Webber address the potential role for pharmacogenomics in cardiac transplantation in their 2015 article in *Circulation*.[12] The review contains several useful tables, including a summary of immunosuppressive agents and the genes associated with drug response and a table highlighting known genetic variances that might impact drug selection and dosing in pediatric cardiac transplant patients. The authors discuss the clinical implications of precision medicine in this patient population, using tacrolimus and azathioprine as examples. They conclude with an interesting section on the ways in which biological factors, such as the higher number of genetic variants in black patients that predispose them to inflammation, can contribute to health disparities and an example of the interface between practitioners and the Vanderbilt University Medical Center Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment that supports the clinical use of pharmacogenomics at their institution.

Epilepsy

Recent genetic advances and their potential use precision medicine for children with severe forms of epilepsy were examined by Mudigoudar and colleagues in an article for *Seminars in Pediatric Neurology*.[13] While the paper primarily focuses on current treatment of infantile spasms, Dravet syndrome, and Lennox-Gastaut syndrome, the authors conclude with a discussion of emerging therapies in rare epilepsies. The importance of pharmacogenomics research is highlighted by a review of several recent examples, such as the use of sirolimus (rapamycin) in patients with tuberous sclerosis complex (SC1 and TSC2) associated with mammalian target of rapamycin (mTOR) loss-of-function mutations. Another example is the recognition of mutations in GRIN2A, which encodes a subunit of NMDA receptors, in patients with early onset epileptic encephalopathies that led to an open label trial of memantine which demonstrated improvement in seizure control. Other examples include studies using quinidine for patients with epilepsy of infancy with migrating focal seizures (EIMFS) associated with mutations in the potassium channel KCNT1, and phenytoin for patients with early infantile epileptic encephalopathies associated with voltage-gated sodium channel (SCN2A and SCN8A) mutations.

A 2015 paper by Nakashima and colleagues describes the first pharmacokinetic-pharmacodynamic model to identify optimal valproic acid trough concentrations in the treatment of epilepsy.[14] A total of 77 pediatric and adult patients were included in the analysis. A nonlinear mixed-effects model was found to best represent the relationship between trough concentrations and successful treatment, defined as a $\geq$ 50% reduction in seizures. The model was fitted using a logistic regression model, with age, seizure locus, sodium channel neuronal type 1 alpha subunit rs3812718 polymorphism, and the administration of other antiepileptics (carbamazepine, clonazepam, phenytoin, and topiramate) associated with treatment success. Use of the model allowed calculation of the optimal trough concentration for each patient in the study. The authors conclude that these findings may contribute to the development of personalized pharmacotherapy for epilepsy.

Infectious Diseases

Voriconazole is the antifungal of choice for young children with invasive aspergillosis. In a new paper from *Antimicrobial Agents and*

Chemotherapy, Huurneman and colleagues describe the pharmacokinetic-pharmacodynamic model they developed to aid in identifying an individual child's optimal voriconazole dose based on changes in galactomannan levels.[15] Much is known about voriconazole pharmacokinetics in children, and therapeutic drug monitoring is routinely used to ensure adequate plasma concentrations and minimize toxicity. The relationship between serum concentrations and therapeutic success, however, has not been established.

The authors used an existing pharmacokinetic model to estimate the average area under the concentration time curve (AUC) from 261 voriconazole concentrations obtained from 12 children. Thirty-three galactomannan levels, a biomarker for voriconazole efficacy, were also available from the children. This information was then used to determine the relationship between the ratio of AUC to the concentration that induced half maximal killing (AUC/EC_{50}) and the patient's terminal galactomannan level. The ratio $(AUC/EC_{50})/15.4$ accurately predicted the terminal galactomannan ($p = 0.003$), with a ratio > 6 indicative of a lower galactomannan level, reflecting treatment success. The authors intend to develop software using the model to maximize clinical efficacy by enabling individualization of voriconazole dosing.

Pain Management

Jimenez and Galinkin published a provocative review in the July 2015 issue of *Anesthesia and Analgesia* on the use of pharmacogenetics, genomics and proteomics to improve our ability to predict children's response to analgesics.[16] The authors begin the paper with a review of the pediatric literature on the variability in codeine response resulting from CYP2D6 polymorphisms. Ultrarapid metabolizers are at risk for opioid toxicity as the result of conversion to higher concentrations of morphine and morphine-6-gluronide, while poor metabolizers may experience inadequate analgesia as the result of less morphine production. Wild type (normal function) alleles occur in approximately 71% of Caucasians of European descent, compared to 50% of Asians and African-Americans. East Africans are the most likely to have the CYP2D6 ultrarapid metabolizer phenotype and are more likely to be at risk for opioid toxicity.

The authors also discuss the effects of polymorphisms or mutations in genes affecting response to morphine, including the UGTB7 gene involved in morphine metabolism, the OPRM1 gene coding for the mu-opioid receptor, and genes coding for transport proteins that control passage across the blood-brain barrier (ABCB1) and a hepatic uptake transporter (OCT1). They highlight an earlier study of 194 children receiving morphine after tonsillectomy/adenoidectomy that found a lower morphine clearance and more adverse effects in the Caucasian children compared to the African-American children.[17] The authors of the study hypothesize that this may be the result of polymorphisms in the OCT1 gene. Studies including Latino children have found a higher incidence of adverse effects in these patients compared to Caucasian children without evidence of differences in polymorphisms or other pharmacogenomic differences, suggesting that further research is needed in this patient population to identify the source of this difference.

Sickle Cell Disease

Two groups of investigators have recently described use of precision medicine in the treatment of children with sickle cell disease. In a 2015 paper from the *British Journal of Clinical Pharmacology*, Dong and colleagues described the development of a population-based pharmacokinetic model to guide individualized dosing of hydroxyurea.[18] A total of 712 serum concentrations from an earlier clinical trial were used to generate a population pharmacokinetic model. All patients were treated with a single oral 20 mg/kg dose of hydroxyurea followed by individualized dosing until the maximum tolerated was achieved. This dose was then continued for another 3 months of treatment. Serial timed plasma samples were collected on day 1 and during the maintenance phase. Non-linear mixed-effects modelling was used to estimate individual pharmacokinetic parameters and hydroxyurea exposure (AUC). Body weight and cystatin C were identified as significant predictors of hydroxyurea clearance. Based on the model, a suggested protocol for patient serum sampling would include a baseline sample and samples at 15-20 minutes, 50-60 minutes, and 3 hours after an initial 20 mg/kg oral dose. The mean goal AUC was 115 mg/L/hr. This model-based approach to individualized dosing is currently being studied in the prospective Therapeutic Response Evaluation and Adherence Trial (TREAT). Details are available at https://clinicaltrials.gov/ct2/show/NCT02286154?term=treat+hydroxyurea&rank=1.

In the July 2016 issue of *Pediatrics*, Gammal and colleagues described the results of an ongoing clinical trial of preemptive pharmacogenetic testing at St. Jude Children's Research Hospital.[19] All children with either a

prescription or an inpatient medication order for codeine are eligible for CYP2D6 genotyping in their program. A total of 2,468 children have been evaluated since the inception of the program in 2011, including 830 with sickle cell disease. Ninety-seven percent of these patients were African-American, and they ranged in age from 9 months to 18 years. Genotyping revealed that 1.4% of the patients were poor metabolizers and 7% were ultrarapid metabolizers, consistent with previous population studies. The authors noted that 87% of their patients had no gene mutations or copy variation and were given standard doses of codeine without adverse effects. The poor and ultrarapid metabolizers were treated with alternative analgesics. The authors concluded that preemptive pharmacogenetic testing was a rational approach to guide analgesic use in patients with sickle cell and prevented avoidance of an otherwise useful analgesic in this patient population.

Pharmacogenomics in Practice

A new paper from Bowdin and colleagues at the SickKids Genome Clinic describes their interprofessional approach to incorporating pharmacogenomic data into patient care in the clinic setting.[20] The paper provides and in-depth look at the challenges and benefits of developing a clinic to focus on individualized therapy based on pharmacogenetic data. The authors address currently available laboratory testing and the challenges of obtaining clinically relevant data in a useful format, as well as the need for collaboration among clinics. They also highlight the need for genetic counseling and call attention to the potential impact of testing on future employment and insurance coverage. This article will be a useful resource for clinicians starting to use pharmacogenomics in their practice.

Summary

The growing body of research in precision medicine, particularly in the area of pharmacogenomics, includes studies in both children and adults. While findings from these studies now inform dosing and monitoring recommendations for several drugs used in children, the ability to integrate this information into routine patient care and fully realize the benefits of precision medicine remains a future goal.

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