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FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to the 21st issue of ESSENCE.

Drug discovery and development is a long and expensive process involving multiple phases including Target selection and lead development, preclinical development, and then clinical trials. After the Investigational New Drug (IND) passes Phase I where its safety and tolerability are investigated, it enters Phase 2 clinical trial. About 70% of drugs enter phase 2 trials from Phase 1. The current issue highlights the important elements of Phase 2 clinical trials including its Phase 2a and Phase 2b.

Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people. Declining renal function can affect the pharmacodynamics and pharmacokinetics of drugs in many different ways and hence a individualised drug dosage regimen is crucial in these patients. The current issue addresses this aspect including the calculation of drug doses in patients of renal impairment.

This issue also has a guest article on SHINE Trial which investigated a shorter treatment for Minimal Tuberculosis in Children. It found that a shorter course of four months was as effective as the standard six-month regimen.

Further, as always, the current issue has new drug approvals, interesting news from the world of medicines, crossword puzzle on Drugs causing 'Acute/Chronic Interstitial Nephritis' and the cartoon corner.

We hope you enjoy reading it.

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Phase 2 Clinical trials: An Overview

Drug discovery and development is a long and expensive process involving multiple phases including Target selection and lead development, preclinical development, and then clinical trials. Once a candidate molecule has successfully passed the pre-clinical (Invitro and animal) phase, it is designated as Investigational New Drug (IND) and enters the phases of clinical trial to study its effect on humans. Various phases of clinical trials (phase 0- phase 3) need to be conducted extensively to evaluate efficacy and safety. After the IND passes Phase I where its safety and tolerability are investigated, it enters Phase 2 clinical trial. About 70% of drugs enter phase 2 trial from Phase 1.

While Phase 1 trial is conducted in healthy volunteers to investigate the safety and tolerability, phase 2 clinical trial is primarily focussed on therapeutic efficacy of the drug in patients to study whether or not the drug may ultimately benefit patients. Phase 2 trials are usually randomized, controlled studies and involve participants selected using clear inclusion and exclusion criteria, to allow close monitoring of a relatively homogenous patient population and may last from few months to almost two years.

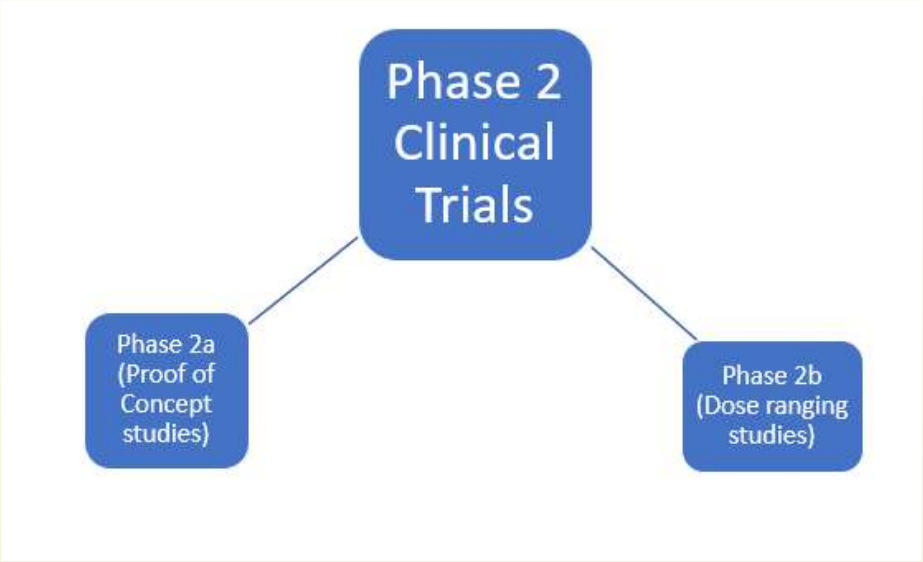
Effect of the drugs in different doses is one of the main goals of phase 2 trials and helps determine an appropriate dose and treatment regimen that can be tested in phase 3 trials. The doses used in phase 2 are generally less than the highest of those used in phase 1 and the treatment is given to a larger population of people in phase 2, usually 100 to 300 patients.

Phase 2a and Phase 2b:

It is only in Phase 2 that an IND is first tested in patients with the disease of interest and may drugs fail at this stage due to lack of efficacy. This can be very expensive in terms of time and money for the pharmaceutical company developing the drug. Hence, many times, to quickly test the effectiveness of a drug and arrive at a 'go/no go' decision 'proof of concept' studies are done to see the response of the drug before further more expensive studies are conducted. These are also called as Phase 2a, focused on therapeutic exploration. These are usually randomised, single blinded, placebo control, parallel group design in a small number of patients (100-200).

In Phase 2a, the drug is usually tested at the maximum tolerated dose (MTD- as determined in Phase 1 trial) in order to minimise false negative results, maximise the pharmaco-dynamic effect and provide the best test of hypothesis. The results of Phase 2a will determine whether it is worthwhile to proceed to further stages or abandon the drug development.

If the phase 2a studies are positive (proven concept) , the drug enters the Phase 2b trials which are designed specifically to rigorously test the efficacy of the drug in a different doses (dose ranging studies) in the given disease condition. Here, the drug is given in incremental doses, starting from much lower than MTD, to see the efficacy of the drug at each dose range. Phase 2b trials are usually larger than Phase 2a, with 200-400 participants, randomised, double blind parallel placebo/active control trials. These evaluate potential study end points, target populations and recommended doses that can be used in further Phase 3 clinical trials.



Conclusion:

Phase 2 trials are able to provide information regarding the safety and efficacy of a drug in a given patient population, while also helping to decide the dose-responsiveness of the drug that helps in further phase 3 clinical trials. Only about 33 percent of experimental drugs which show promising results usually clear phase 2 and will go on to Phase 3 trial.

References:

1. Torres-Saavedra PA, Winter KA. An Overview of Phase 2 Clinical Trial Designs. Int J Radiat Oncol Biol Phys. 2022 Jan 1;112(1):22-29.
2. U.S. Food and Drug Administration (FDA). *Step 3: Clinical Research*. The Drug Development Process; https://www.fda.gov/patients/drug-development-process/step-3-clinical-research.

Recent new/Update from the world of medicines ….

A new antibiotic, discovered with AI, may defeat antibiotic-resistant Acinetobacter

Using artificial intelligence, researchers say, they've found a new type of antibiotic that works against a particularly menacing drug-resistant bacteria. When they tested the antibiotic on the skin of mice that were experimentally infected with the superbug, it controlled the growth of the bacteria, suggesting that the method could be used to create antibiotics tailored to fight other drug-resistant pathogens. The researchers also tested the antibiotic against 41 different strains of antibiotic-resistant Acinetobacter baumannii. The drug worked on all of them, though it would need to be further refined and tested in human clinical trials before it could be used in patients. What's more, the compound identified by AI worked in a way that stymied only the problem pathogen. It didn't seem to kill the many other species of beneficial bacteria that live in the gut or on the skin, making it a rare narrowly targeted agent.

First 'gene silencing' drug for Alzheimer's disease

The trial, led by consultant neurologist Dr Catherine Mummery (UCL Queen Square Institute of Neurology & the National Hospital for Neurology and Neurosurgery), represents the first time that a 'gene silencing' approach has been taken in dementia and Alzheimer's disease. The approach uses a drug called BIIB080 (/IONIS-*MAPTRx)*, which is an antisense oligonucleaotide (used to stop RNA producing a protein), to 'silence' the gene coding for the tau protein -- known as the microtubule-associated protein tau (MAPT) gene. This prevents the gene from being translated into the protein in a doseable and reversible way. It will also lower the production of that protein and alter the course of disease. Further trials will be needed in larger groups of patients to determine whether this leads to clinical benefit, but the phase 1 results published in *Nature Medicine* -- with results from 46 patients -- are the first indication that this method has a biological effect.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Minocycline	Risk of agranulocytosis
2.	Nifedipine	Risk of pulmonary oedema when used in pregnancy
3.	Methylphenidate	Potential risk of birth defects and malformations
4.	Ivermectin	Potential risk of encephalopathy
5.	Pregabalin	Risk of severe respiratory depression
6.	Sertraline	Potential risk of microscopic colitis

Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people, and more than 1 million of them are receiving kidney replacement therapy. Uraemia generally reduces glomerular filtration and/or active secretion, which leads to a decrease in renal drug excretion resulting in a longer elimination half-life of the administered drug. In addition to changing renal elimination directly, uraemia can affect drug pharmacokinetics in unexpected ways. For example, declining renal function leads to disturbances in electrolyte and fluid balance, resulting in physiologic and metabolic changes that may alter the pharmacokinetics and pharmacodynamics of a drug. Both therapeutic and toxic responses may be altered as a result of changes in drug sensitivity at the receptor site. Overall, uremic patients have special dosing considerations to account for such pharmacokinetic and pharmacodynamic alterations.

In clinical practice, estimation of the appropriate drug dosage regimen in patients with impaired renal function is based on an estimate of the remaining renal function of the patient and a prediction of the total body clearance. A complete pharmacokinetic analysis of the drug in the uremic patient may not be possible. Moreover, the patient's uremic condition may not be stable and may be changing too rapidly for pharmacokinetic analysis. Each of the approaches for the calculation of a dosage regimen has certain assumptions and limitations that must be carefully assessed by the clinician before any approach is taken.

Calculation of Creatinine Clearance from serum creatinine

Based on the patient's age, height, weight, and gender, the more precise techniques are used. When estimating creatinine clearance from serum creatinine concentration, the Cockcroft and Gault (1976) method is utilized. This approach takes into account the patient's age and weight.

$$Cl_{cr} = \frac{[140 - \text{age(year)}] \times \text{body weight (kg)}}{72\ (C_{cr})}$$

For females, use 90% of the Clcr value obtained in males. In some hospitals, 85% is used for female subjects.

Estimated GFR (eGFR) Using Modification of Diet in Renal Disease (MDRD) Formula or Using the Chronic Kidney Disease – Epidemiology Collaboration (CKD–EPI) Equations

The most popular IDMS traceable equations for calculating GFR in patients over the age of 18 are those from the Modification of Diet in Renal Disease (MDRD) Study and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

GFR was estimated using the MDRD Study equation re-expressed for use with the serum creatinine values standardized to isotope dilution mass spectroscopy: GFR = 175 × standardized $S_{cr}^{-1.154}$ × $age^{-0.203}$ × 1.212 (if black) × 0.742 (if female), where S_{cr} is serum creatinine.

The CKD-EPI equation, expressed as a single equation, is GFR = 141 × min (Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] _ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κor 1, and max indicates the maximum of Scr/κ or 1

It has been suggested that the recently developed CKD-EPI equation, which is used to estimate GFR, is more accurate than the MDRD equation, particularly when GFR is high. Additionally, it demonstrates reduced bias, increased precision, and increased accuracy.

Basis for Dose Adjustment in Uraemia

The loading drug dose is calculated based on the patient's apparent volume of distribution. It is generally assumed that the apparent volume of distribution is not altered significantly, and therefore the loading dose of the drug is the same in uremic patients as in subjects with normal renal function. Based on the patient's drug clearance, the maintenance dose is determined. The rate of renal medication excretion has decreased in the uremic patient, which has caused a drop in the body's overall clearance. The majority of strategies for dosage modification presuppose that nonrenal drug clearance is unaltered. Creatinine clearance is used to evaluate how much of the uremic patient's kidneys still function normally. After estimating the patient's remaining total body clearance, a dosage regimen can be created by either lowering the maintenance dose, raising the dosing interval, or modifying both the maintenance dose and dosage interval. Although total body clearance is a more accurate index for drug dosing, the elimination half-life of the drug is more commonly used for dose adjustment because of its convenience. While the elimination half-life provides information on the amount of time needed to attain steady state concentration, clearance enables the prediction of drug concentrations at steady state.

To conclude, renal function may be assessed by several methods. Creatinine clearance based on the serum concentration of endogenous creatinine is used most often to measure glomerular filtration rate. Creatinine clearance values must be considered carefully in special populations such as elderly, obese, and emaciated patients. The Cockcroft–Gault method is frequently used to estimate creatinine clearance from serum creatinine concentration. Dose adjustment in renal disease is based on the fraction of drug that is really excreted and generally assumes that nonrenal drug elimination remains constant. Different approaches for dose adjustment in renal disease give somewhat different values.

References:

1. Bennett WM. Guide to drug dosage in renal failure. Clin Pharmacokinet 1988;15:326–354.

2. Bjornsson TD: Nomogram for drug dosage adjustment in patients with renal failure. Clin Pharmacokinet 1986;11:164–170.

New Drug Approvals…

Omaveloxolone is an activator of Nrf2 (nuclear factor erythroid 2–related factor 2) approved for the treatment of Friedreich's ataxia. The recommended dose 150 mg orally once daily.

Tofersen is an antisense oligonucleotide approved for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene. The recommended dose is 100 mg per administration intrathecally. Initiate treatment with 3 loading doses administered at 14- day intervals. A maintenance dose should be administered once every 28 days thereafter.

Leniolisib is a kinase inhibitor approved for the treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS). The recommended dose is 70 mg orally twice daily.

Fezolinetant is a selective neurokinin 3 (NK3) receptor antagonist approved for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. The recommended dose is 45 mg orally once daily.

Cartoon Corner…

Excerpt from "Drug Autobiographies in Pharmacology" by Dr. Sushil Sharma

The majority of TB cases in children are less severe than those in adults. Children with TB may respond well to treatment plans that are shorter than those for adults, however there is still a lack of strong evidence to support this. Shorter treatment courses may be less hazardous, less likely to cause drug-drug interactions in children living with HIV, and less likely to cause adherence issues, all of which can reduce costs to families and health systems. Shorter, safe and effective treatment regimens need for children with drug-susceptible TB.

The SHINE study (Shorter Treatment for Minimal Tuberculosis in Children) was the first and only significant phase three trial to assess how long pediatric patients with non-severe drug-susceptible TB should receive treatment. This trial was a multi-center, open-label, parallel-group, non-inferiority, randomized, controlled, two-arm trial comparing 4-month (16 weeks) versus the standard 6-month (24 weeks) treatment durations in children under 16 years of age with symptomatic non-severe TB. Rifampicin, isoniazid, and pyrazinamide were administered to children and young adolescents under the age of 16 at WHO-recommended doses that were suitable for pediatric dosing.

PICO question: In children and adolescents with non-severe TB, should a 4-month intervention regimen versus the standard 6-month regimen conforming to WHO guidelines be used?

Evidence: In the SHINE trial, the primary efficacy outcome was a composite of treatment failure (including an extension of therapy beyond replacing missed doses, TB treatment drug changes or restarts due to suspected treatment failure), on-treatment loss-to-follow-up, TB recurrence, or death by 72 weeks (from randomization), excluding children not reaching 16 weeks of follow-up (modified-intention-to-treat). The non-inferiority margin for the primary efficacy result was 6%. The primary safety result was grade 3-5 adverse events recorded during TB treatment.

The SHINE trial defined non-severe TB as peripheral lymph node TB or respiratory TB (including simple intrathoracic lymph node disease) limited to one lobe without cavities, no substantial airway obstruction, uncomplicated pleural effusion, and no miliary TB.

The SHINE trial inclusion criteria were: children and young adolescents aged <16 years; weight ≥3 kg; no known drug resistance; symptomatic but non-severe TB; smear negative on gastric aspirate or other respiratory sample (an Xpert MTB/RIF positive, rifampicin susceptible result was allowed); clinician's decision to treat with a standard first-line regimen; not treated for TB in the previous two years; known HIV status (positive or negative). Trial exclusion criteria were: respiratory sample acid fast bacilli smear-positive (a smear-positive peripheral lymph node sample was allowed); premature birth (<37 weeks) and aged under 3 months; miliary TB, spinal TB, TBM, osteoarticular TB, abdominal TB, congenital TB; pre-existing, non-tuberculous disease likely to prejudice the response to, or assessment of, treatment (such as liver or kidney disease, peripheral neuropathy or cavitation); any known contraindication to taking TB drugs; known contact with a drug-resistant

in the child; being severely ill; pregnancy.

A total of 1204 children were enrolled in the trial between July 2016 and July 2018. The median age of enrolled children was 3.5 years (range: 2 months – 15 years), 52% were male, 11% had HIV-infection, and 14% had bacteriologically confirmed TB. Retention in the trial by 72 weeks and adherence to allocated TB treatment were 95% and 94%, respectively. Sixteen (2.8%) versus 18 (3.1%) children reached the primary efficacy outcome (treatment failure) in the 16- versus 24-week arms respectively, with an unadjusted difference of −0.3% (95% CI: −2.3, 1.6). Treatment success was reported in 97.1% of participants receiving the 16-week regimen versus 96.9% in those receiving the 24-week regimen (relative risk (RR): 1.00, 95% CI: 0.98–1.02). Non-inferiority of the 16-week regimen was consistent across all intention-to-treat, per-protocol and key secondary analyses. This included restricting the analysis to the 958 (80%) children that were independently adjudicated to have TB at baseline by the trial Endpoint Review Committee. A total of 7.8% of children experienced a grade 3–5 adverse event in the 16-week arm, versus 8.0% in the 24-week arm (RR: 0.98, 95% CI: 0.67–1.44). There were 115 on-treatment grade ≥3 adverse events in 95 (8%) children, 47 (8%) in the 16-week and 48 (8%) in the 24-week arm, most common being pneumonia or other chest infections (29 (25%)) or liver-related events (11 (10%)) across both arms. There were 17 grade 3 or 4 adverse reactions (considered possibly, probably or definitely) related to trial drugs, including 11 hepatic events; all adverse reactions except three occurred in the first eight weeks of treatment.

GDG considérations : The GDG judged that while the desirable effects related to this PICO question are related to treatment outcomes, shortening the duration of treatment is also important and desirable (as reducing the length of treatment could make treatment easier for children and caregivers as well as reduce cost for families and the health system). The GDG discussed that since the SHINE trial was a non-inferiority trial, no difference in unfavorable outcomes between the two arms is what the trial aimed to detect. Therefore, both desirable and undesirable effects were judged by most GDG members as trivial. Since non-inferiority of the 4-month regimen was demonstrated in the trial, the balance of effects was judged to not favor either the shorter or the longer duration of treatment.

Reference:

1. Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, et al; SHINE Trial Team. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. N Engl J Med. 2022 Mar 10;386(10):911-922.

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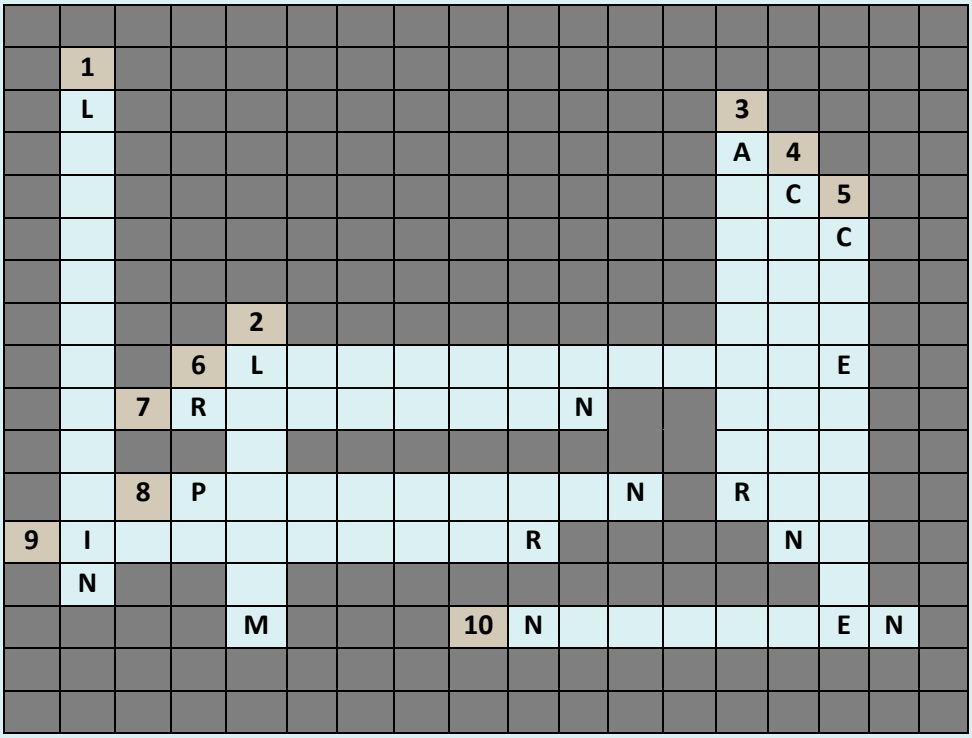
Crossword Puzzle… ***Hint:*** *Drugs Causing Acute/Chronic Interstitial Nephritis*



Downward	**Across**
1. Second generation fluoroquinolone (*12*) 2. Antimaniac Dug (*7*) 3. Antiviral drug used against herpes infections (*9*) 4. Anticancerous platinum compound (*9*) 5. H_2 Receptor blocker used in peptic ulcer disorders (*10*)	6. Proton pump inhibitor used in PUD (*12*) 7. First line Antitubercular drug *(8)* 8. Antiseizure drug associated with gingival hyperplasia *(9)* 9. Protease inhibitor used in HIV infection *(9)* 10. NSAID which is derived from Propionic acid *(8)*

Answer to the Crossword Puzzle (21st Issue) is given below:

Downward

1. Levofloxacin 3. Acyclovir 5. Cimetidine
2. Lithium 4. Cisplatin

Across

6. Lansoprazole 8. Phenytoin 10. Naproxen
7. Rifampin 9. Indinavir