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Single dose formulations in the era of fixed dose combinations for TB: role in clinical trials

Dear Editor,

A recent article by Sotgiu et al. highlighted shortages in anti-TB drug supply, its impact on the TB treatment and implications for National TB programmes (NTPs).[1] The authors raised various concerns, including unfavourable treatment outcomes, drug toxicities, resistance and catastrophic costs.[1] We address another aspect of the lack of availability of anti-TB drugs, which impacts TB research globally. The need for newer treatment regimens with different doses of the recommended drugs or newer drugs for the management of all forms of TB is being explored globally. This includes adjusting doses of recommended drugs, replacing drugs based on pharmacokinetics and available evidence, or due to the development of drug resistance. For example, evidence suggests that higher doses of rifampicin may improve treatment outcomes in drug-sensitive TB (DS-TB).[2] The currently recommended drugs for severe forms of TB such as tuberculous meningitis (TBM) have varying cerebrospinal fluid (CSF) penetration. Isoniazid and pyrazinamide achieve optimal therapeutic levels, whereas rifampicin and ethambutol achieve subtherapeutic levels in the brain.[3] Drugs such as ethionamide and fluoroquinolones have demonstrated good CSF penetration. Mortality and morbidity associated with TBM tend to be high despite treatment. We therefore need to evaluate the optimal regimen for fatal diseases like TBM. Currently, the role of intensified shorter regimens for various forms of TB is a key area of focus in TB research.

WHO recommends fixed-dose combinations (FDCs) for the management of DS-TB for 6 months. FDCs have similar efficacy and patient satisfaction as compared to single-dose formulations (SDFs).[4] However, the role of SDFs in TB management is significant, particularly in specific clinical scenarios (Figure). Clinical trials evaluating higher doses of the recommended drugs require SDFs to achieve the appropriate dosage. Similarly, trials on reconstituted regimens warrant the usage of SDFs. Ongoing trials, like RIAlta Phase 2b/c for pulmonary TB and INSHORT for TBM, plan to use FDCs along with SDFs to compensate for the higher dose of rifampicin.[5,6] The INSHORT trial is a multicentric ongoing randomized clinical trial in India. The intervention arms in the INSHORT trial include high-dose rifampicin (25 mg/kg), moxifloxacin instead of ethambutol for two months and pyrazinamide for six months.[6] However, the availability and procurement of SDFs of first-line anti-TB drugs at various doses to constitute an appropriate weight-based regimen was extremely challenging. Similarly, from our previous experience in a pediatric TBM trial, procurement of pediatric formulations for weight-based dosing also had difficulties.[7]

The SDFs used in trials must be quality assured, with adequate stock maintained for uninterrupted drug supply throughout the trial period. Multi-centric trials also demand a timely drug supply from the central site to other study sites. There could be several reasons for inadequate availability and supply of SDFs, such as limited usage and demand in comparison to FDCs in NTPs, inadequate demand forecasting mechanisms, fragmented supply chain, shorter shelf-lives, or prolonged delivery time.[8] The availability of substandard and falsified anti-TB drugs is another cause for concern, and the extent of the problem globally is largely unknown.[9] Stringent manufacturing regulations, expiry of patents for manufacturing, and diminishing commercial returns often lead to lower productivity of anti-TB drugs.[10] The Global Drug Facility (GDF) promotes access to quality drugs and has enhanced the availability of anti-TB drugs over the years. However, GDF supplies only a limited number of SDFs.

All NTPs should be sensitized to the necessity of SDFs. The GDF should also consider mechanisms to stock more SDFs and supply them to clinical trials on demand. TB researchers globally should come together to advocate for uninterrupted supply through common designated agencies. With the goal of TB elimination by 2035 and numerous unanswered questions

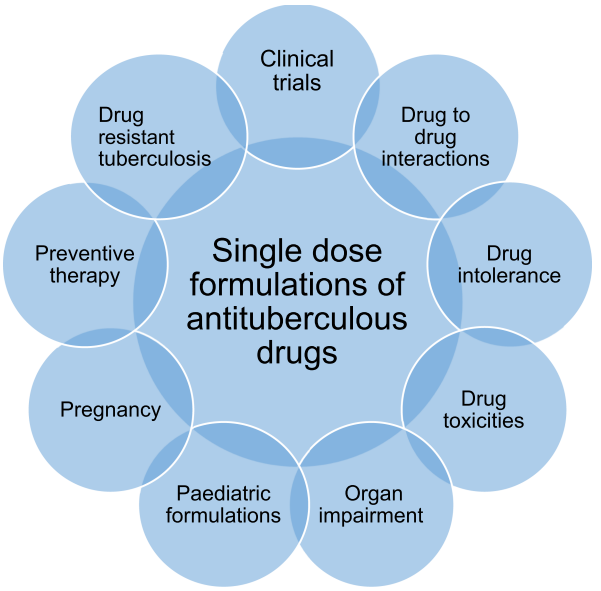

Figure. Role of single-dose formulations in TB management.

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at hand, it is time to revisit the role and availability of SDFs.

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