PERSPECTIVE

Conception of National Biologics Registry for Pediatric Rheumatology: Need of the Hour and the Way Forward

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The outcome for children with rheumatic diseases has been dramatically altered by the use of biological therapies. Increasing use of these agents will need careful monitoring for long term safety, particularly in children. Current data on safety of these drugs stem exclusively from Western literature. There is clear need for a registry of all children with rheumatic diseases who are commenced on biological agents to ensure appropriate pharmacovigilance. In this perspective, we discuss the need for and the role of a biologics registry for children with rheumatic diseases in India.

Key words: Biosimilar, Rheumatic diseases, Safety.

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Scope of Biologics in Clinical Practice

The advent of biological agents has resulted in significant improvement in management and outcomes for patient with rheumatic diseases. Biologicals are biotechnologyderived products of biological origin which can modulate our immune system. Biosimilar or similar biotherapeutic products are the products approved by regulatory agencies based on their demonstration of similarity with the original biological molecule in terms of quality, safety and efficacy [1,2]. Children with rheumatic conditions, which require long-term steroids, experience its sideeffects like growth retardation. With the advent of biologicals targeting specific cytokines, steroid-free remission is increasingly becoming a reality for majority of subjects with underlying rheumatic conditions [1-3]. For instance, 60-90 % of children with JIA who failed disease control with first line conventional disease modifying antirheumatic drugs (cDMARDs) showed significant clinical response with use of biologics [4].

Ever since the approval of first biological agent infliximab, an anti-TNF agent, for rheumatoid arthritis, there has been an exponential growth of biologicals and biosimilar agents for management of many rheumatic disorders [3,5], as well as other conditions such as inflammatory bowel disease, psoriasis etc. [6,7]. More recently, biologics (IL-1, IL-6 antagonists) are being used for curtailing the hyper-inflammatory state due to COVID-19 infection both in adults and children [8].

Challenges in the Use of Biologics and A Ray of Hope

The original biological molecules are cost prohibitive, particularly in low- and middle-income countries (LMICs). Subsequent to expiry of patents for original biological molecules, various economical biosimilar agents have emerged. In India, guidelines on biosimilar is in existence since 2012, and many of the biologicals and biosimilar agents are gradually coming under the ambit of reimbursement schemes funded by central and state governments [2]. Another potential development in this regard is the discovery of small molecules such as Janus kinase (JAK) inhibitors. The annual cost of generic tofacitinib for a 40 kg child in India currently is approximately INR 1300-1500/month, compared with INR 250000 for adalimumab [9]. JAK inhibitors have the advantage of oral administration, which is particularly important for children.

Advantages of Registries: Slating the Ground Realities

Even though the efficacy of biological agents has been proven in well-designed randomized controlled trials (RCTs), the results of these trials reflect outcome in controlled study settings, within a limited time frame, thereby restricting their generalizability and their ability to detect rare adverse events. Unlike RCTs, registries have the potential to record the long-term outcomes of these drugs as well as data regarding drug survival, cost

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Box I Key Observations From Pediatric Biologic Registries

German Registry for Biologics in Pediatric Rheumatology (BiKeR registry) [18,22-24]

- Use of TNF, IL-1 or IL-6 inhibitors is associated with increased risk of infections.
- Cytopenias and hepatic events were associated with tocilizumab and canakinumab.
- No increased risk for malignancies, uveitis or other autoimmune disorders except inflammatory bowel disease.
- Childhood Arthritis and Rheumatology Research Alliance (CARRA registry) [19]
- Use of TNFi was associated with increased risk of psoriasis.
- Pharmachild registry [25]
- Observed significant number of opportunistic infections in JIA patients on immunosuppressive therapy.
- British Society for Pediatric and adolescent Rheumatologists (BSPAR), BiKeR and Pharmachild registry [26]
- · Comorbidities like varicella, tuberculosis and uveitis were reported.

TNF; tumor necrosis factor, IL; interleukin, TNFi; tumor necrosis factor inhibitor.

implications, immunogenic events and barriers to the use of these agents in real-life settings over many decades [6,10]. For monitoring the pattern of adverse effects of biologics, various biological registries are operational in UK, Europe and America e.g., German registry for biologics in pediatric rheumatology (BiKeR), Italian Lombardy rheumatology network (LORHEN) registry, Danish DANBIO registry, Spanish BIOBADASER registry and British Society of Rheumatology Biologics Register (BSRBR) [6,11-13]. The key observations from some of the major pediatric registries, which bear a clinical implication on day-to-day practice, are summarized in **Box I**.

Indian Scenario

It is unfortunate that such biologic registries are not in existence in LMIC settings like ours, despite widespread availability and use of these agents. Isha, et al. [14], in a case series of 11 subjects, demonstrated the efficacy of biologics in JIA; however, the study was not designed to capture long term safety signals with use of biologics. The increased risk of infection, particularly reactivation of latent tuberculosis, is a major concern with use of TNF inhibitors in endemic regions like India, with data from adult population having demonstrated an approximately four-fold increase in tuberculosis in those exposed to anti-TNF compared with TNF naïve subjects with rheumatoid arthritis [15]. In the authors' own experience, the reactivation of latent tuberculosis with anti-TNF may have fatal complications [16]. The high background rate of tropical infections and latent tuberculosis [17], coupled with other challenges like unregulated prescription practices and variable follow up, demands for a biological registry in our country. Setting up a biological registry would not only help in capturing the outcome and safety of biological agents in the long-term, but also can be used for cost analysis, evaluating the barrier to compliance and thus would prove pivotal in framing guidelines for judicious use of these agents in resource limited settings.

Though setting up a pediatric biologic registry in LMIC settings would offer numerous advantages as highlighted above, its inception and maintenance foresees challenges such as funds, manpower and inter-institutional coordination. Registries such as BiKeR [18], Pharmachild [19], CARRA [20] are funded by industry and supported by non-governmental organizations and the government. In our setting, reciprocating the model of industry-academia collaboration seems a viable option, wherein the registries would be funded by industry, while the data acquisition, interpretation and reporting would be led by academic institutions. The Government can help by ensuring industry is required to do this as part of their pharmacovigilance.

Despite the challenges, it seems appropriate to consider a biologic registry in our settings. In an ideal world there should be a national registry for all patients on biologicals across all specialties. We believe that pediatric rheumatology specific registry could be the start, which in time might expand to include children across all specialties that are commenced on novel therapies such as biologics or small molecules. However, to be pragmatic, we propose to conceive a biologic registry for pediatric rheumatology, and the experience from this would gradually take it further to broader spectrum as above.

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