Implications of the first FDA-approved anticoagulant in pediatrics: One ship has sailed but the next ones are at the dock – Highlight On [PBC-19-1346.R2]

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There is no question that developing new medications in children is fraught with challenges, particularly for rare conditions including pediatric venous thromboembolism (VTE). This is due to both logistical and ethical considerations which are nicely described in a document on the Food & Drug Administration (FDA) website.[1] Furthermore, gaining an approval from the FDA for pediatric use requires a functional partnership between pharmaceutical companies (Pharma), academia, and the regulators/officers at the FDA. When this relationship works well, novel agents can be made available to children that have the assurance of efficacy and safety which is in the best interest of all involved parties, especially patients. The licensure of emicizumab for the prevention of bleeding in hemophilia A patients is one excellent example in which a serious unmet need for a rare disease was addressed in a timely manner (˜18 months from the start of a phase 3 trial to approval), and where the labelled indication even includes the word "newborn" with respect to the included age groups. [2,3]

Unfortunately, this is not the case with respect to anticoagulants in children, and there is plenty of blame to go around including Pharma, academia (myself included), but also the FDA. I know this all too well as I have had a front seat view having served as an advisor to the FDA on this very topic in 2011 as well as on several other occasions involving specific discussions regarding fondaparinux and rivaroxaban. Although the authors and investigators of this report [4] are to be commended for the significant effort it took to achieve an FDA-approved indication, one can't help but feel that with respect at least to injectable anticoagulants that "the ship has sailed." What do I mean by this? Enoxaparin is the most commonly used low molecular weight heparin (LMWH) and anticoagulant in children with fondaparinux also gaining more use with the prime advantage being that it is a once-a-day option. Despite dalteparin (a less commonly used LMWH) now being licensed for children [5], I doubt it will ever supersede enoxaparin in prescriptions nor does it have the advantages of fondaparinux, particularly once daily dosing.

How did we arrive at such an unenviable situation? Certainly, it is nobody's fault that enoxaparin does not have a pediatric indication—the author's clearly explained the fact that enoxaparin came to the market prior to the Pediatric Research Equity Act (PREA), and at this point, despite the sheer volume of data on the pediatric use of enoxaparin, it will likely never be licensed for children. This is not the case, however, for fondaparinux which has been in regulatory limbo with respect to pediatric use for nearly 15 years. This, despite the fact that there is more published data on fondaparinux than dalteparin including a similarly (to dalteparin) designed, prospective, dose-finding, pharmacokinetic, efficacy and safety study [6-8], and the fact that the Pharma companies (the compound has changed hands a few times) have been in discussions with the FDA repeatedly. Unlike with dalteparin, the FDA has placed numerous and pointless hurdles upon the responsible Pharma for capricious reasons succeeding only in potentially putting children at increased risk of harm by, for example, requiring a dose-finding study when the dose of fondaparinux is already well-

established. This is the antithesis of what the FDA should be doing. This unending process of which I have played a significant part as an academician has been nothing short of befuddling. While the FDA clearly went to great lengths to work with the sponsor to have dalteparin approved for children, they owe the pediatric hematology community an explanation on what has gone so wrong with fondaparinux.

So, where does this leave us currently and what would I recommend pediatric hematologists do with the data from this report [4] and the licensure of dalteparin for children? Importantly, off-label use in the pediatric setting is quite common typically ranging around 50% depending on the setting [9] so there is no need for any pediatric treater to fret over prescribing anticoagulants as such. Thus, if you are comfortable using enoxaparin or fondaparinux based on the available data, the collective pediatric experience and your personal experience, then I would advocate that you continue to do so until there are better options (more on that later). If, however, you prefer to prescribe medications per the prescribing information (to the extent possible) and you find the data from this study compelling, then certainly you may choose dalteparin as your anticoagulant of choice for your pediatric patients with VTE.

Above I discussed the current situation, however on a strongly positive note, there has been outstanding cooperation between Pharma, academicians and the FDA when it comes to the development of the direct oral anticoagulants (DOACs) which without a doubt will dramatically change the management of pediatric VTE. While I have been privy to discussions with the FDA regarding rivaroxaban and have served on the steering committee for the rivaroxaban and edoxaban studies, I am also aware of the productive discussions with respect to dabigatran and apixaban. This trilateral collaboration is the epitome of what PREA is for, and in the coming year or two, it is highly likely that several DOACs will be licensed for use in children and will also lead to the availability of pediatric-friendly formulations.

In conclusion, the approval of dalteparin is on the one hand far too little and too late to be of any meaningful clinical use, yet it does set an example of what fruitful pediatric drug development can look like in hematology/oncology (and other specialties as well) particularly for rare diseases. It is incumbent upon the academic community not to request, but in fact to demand that Pharma fund proper studies (not just ones that "check the box"), and that the FDA review data in a fair and reasonable manner such that the future will be filled with more examples like dalteparin and fewer debacles like fondaparinux.

References

1. https://www.fda.gov/drugs/drug-information-consumers/drug-research-and-children [Accessed September 9, 2020]
2. Young G, Liesner R, Chang , Sidonio R, Oldenburg J, Jimenez-Yuste V, Mahlangu J, Kruse-Jarres R, Wang M, Uguen M, Doral MY, Wright LY, Schmitt C, Levy GG, Shima M, Mancuso ME. A multicenter, open-label, phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood 2019; 134: 2127-2138.
3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761083s000lbl.pdf [Accessed September 9, 2020]
4. Merino M, Richardson N, Reaman G, Ande A, Zvada S, Liu C, Hariharan S, De Claro A, Farrell A, Pazdur R. FDA approval summary: Dalteparin for the treatment of venous thromboembolism in pediatric patients. Pediatr Blood Cancer 2020 (in press).
5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020287s072lbl.pdf [Accessed September 9, 2020]
6. Young G, Yee DL, O'Brien SH, Khanna R, Barbour A, Nugent DJ. FondaKIDS: A prospective pharmacokinetic and safety study of fondaparinux in children between 1 and 18 years of age. Pediatr Blood Cancer 2011; 57: 1049-1054.
7. Ko RH, Michieli C, Lira JL, Young G. FondaKIDS II: Long-term follow-up data of children receiving fondaparinux for treatment of venous thromboembolic events. Thromb Res 2014; 134: 643-647.
8. Shen X, Wile R, Young G. FondaKIDS III: A long-term retrospective cohort study of fondaparinux for treatment of venous thromboembolism in children. Pediatr Blood Cancer 2020; 67:e28295.
9. Yackey K, Stukus K, Cohen D, Kline D, Zhao S, Stanley R. Off-label prescribing practices in pediatrics:

An update. Hosp Pediatr 2019; 9:186-193.