THROMBOTECT takes the lead

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Thromboembolic events in children predominantly occur as secondary complications of severe underlying diseases and their treatment, the most important risk factor being the use of central venous catheters (CVC). In spite of the relative high frequency of thromboembolic events in children with CVC, the evidence to date is equivocal as to whether there is benefit of primary thromboprophylaxis in reducing the risk of these events and whether it outweighs the risk of bleeding in sick children.[1]

One population at particular risk of thromboembolic events consists of children receiving induction chemotherapy for pediatric acute lymphoblastic leukemia (ALL). The mechanism implicated in the development of thromboembolic events is hypothesized to be associated with an acquired antithrombin deficiency resulting from treatment with asparaginase. The only randomized trial to date (PARKAA) assessed primary thromboprophylaxis using antithrombin replacement in children with ALL and CVC during induction chemotherapy. However, PARKAA was a feasibility study with limited power and only showed a trend to efficacy of antithrombin replacement.[2]

In the current issue of Haematologica, Greiner *et al.* report on the THROMBOTECT study which was an open-label, randomized controlled trial assessing the efficacy and safety of primary thromboprophylaxis during induction chemotherapy including asparaginase for ALL in children and adolescents, the majority of whom had a CVC.[3] The study, an investigator-initiated study performed within the Berlin-Frankfurt-Munster cooperative group, recruited 949 patients who were randomized to three arms: activity-adapted antithrombin substitution, prophylactic-dose low molecular weight heparin (LMWH), or low-dose unfractionated heparin (UFH) as their standard of care. The low UFH dose was intended to prevent CVC occlusion but presumably did not achieve a systemic antithrombotic effect, so this arm might be considered a placebo arm. The primary efficacy outcome was symptomatic thromboembolic events, the principal safety outcome was bleeding, assessed during both induction and consolidation chemotherapy. Secondary safety outcomes were event-free survival and overall survival from the underlying ALL.

The results of the study show a significant reduction in the incidence of thromboembolic events with use of antithrombin (1.9%) and LMWH (3.5%) compared to UFH (8.0%). Since a large proportion of children assigned to LMWH crossed over to other arms, an as-treated analysis was performed, showing approximately equal reductions in thromboembolic events risk for antithrombin and LMWH compared to UFH. The incidence of bleeding was low (0.9%) and not different between the three arms. Regarding leukemia outcome, there was an increased relapse rate in children randomized to antithrombin when compared to those randomized to UFH in the intention-to-treat analysis, but no difference in the as-treated analysis. The authors conclude that thromboprophylaxis should be recommended during ALL induction therapy and, given the unclear effect of antithrombin substitution on leukemia outcome, they recommend LMWH as the primary choice at present.

The THROMBOTECT study is an important breakthrough, as it is the first adequately powered randomized trial of primary thromboprophylaxis in pediatric patients. The study shows that thromboprophylaxis with antithrombin or LMWH is effective at preventing thromboembolic events without increasing the risk of bleeding. The THROMBOTECT collaborators can be commended for their outstanding effort in completion of this important study, which will improve the care of children with ALL. Moreover, the study serves as proof-of-concept for thromboprophylaxis in children in other clinical settings. The completion of the study will not only have a significant impact on clinical management, but will also demonstrate that pediatric clinical trials of anticoagulation can be completed.

As with all clinical trials, particularly in children, there are limitations to the study. First, the study was not masked for practical and ethical reasons, as this would have required placebo subcutaneous injections which would have been unacceptable to children and caregivers. The lack of masking increased the potential for cross-over between treatment arms, diminishing the distinction between arms. Of the patients assigned to LMWH, 33% refused the intervention after randomization because of the subcutaneous injections, of whom approximately two-thirds received UFH or no thromboprophylaxis and one-third were given antithrombin substitution. The study design is problematic in that patients who crossed over were allowed to choose between treatment arms, creating an additional source of selection bias. However, the intention-to-treat and the as-treated analyses are reasonably concordant, so the reduction in risk of thromboembolic events with antithrombin and LMWH thromboprophylaxis is still valid.

Second, the open-label study treatment, in combination with the primary outcome being clinically symptomatic thromboembolic events, implies a risk of diagnostic suspicion bias in outcome assessment. Although clinically suspected thromboembolic events were required to be confirmed by objective radiographic imaging, neither attending physicians nor radiologists were masked to treatment allocation. Moreover, there was no central independent adjudication of outcome events.

Third, THROMBOTECT provides information regarding only symptomatic thromboembolic events. However, previous studies in children with ALL and CVC have shown relatively low frequencies of symptomatic thromboembolic events but substantial frequencies of asymptomatic thromboembolism detected by systematic radiographic screening.[2] While some believe that symptomatic thromboembolic events are clinically most relevant, many of the patients with asymptomatic thromboembolism in PARKAA had significant degrees of venous occlusion. The THROMBOTECT study did not include radiographic screening (e.g. ultrasound) which would have achieved a more complete identification of both symptomatic and asymptomatic thromboembolism. Moreover, using objective radiographic screening would have reduced the potential for observer bias. To what extent thromboprophylaxis affects asymptomatic thromboembolism, remains open.

Fourth, while the patients received thromboprophylaxis only during the induction phase they were followed for thromboembolic events and bleeding outcomes into the consolidation phase. One fifth of thromboembolic events and half of the bleeds occurred during induction consolidation. Therefore, as the study interventions had already been discontinued, their association with these outcome events cannot be definitively determined.

The manuscript presents an exploratory subgroup analysis based on age. In children >6 years, frequencies of thromboembolic events were higher (6.4%) and differences between treatment arms more pronounced, while in younger children, thromboembolic events were observed less frequently (2.7%) and not significantly different between arms. This possible age effect should be interpreted with caution, because thromboembolic events may not be detected in younger children as symptoms may be reported to a lesser extent. Treatment effects were qualitatively not different for younger children, and a benefit from anticoagulant prophylaxis, even if smaller, may be extrapolated from older children. Given that there were few bleeding events, using thromboprophylaxis in children of all ages appears reasonable.

One notable observation made in the THROMBOTECT study was the large proportion of children/families that refused LMWH due to subcutaneous injections. Of eligible patients at participating centers, 38% would not consent to enter the study. Among consenting participants, of those randomised to LMWH, 33% refused this treatment due to subcutaneous injections. While the difficulty in treating children with subcutaneous drugs is well known by pediatricians, the THROMBOTECT study provides solid evidence documenting the magnitude of the problem and concludes that there are problems with compliance with anticoagulant drugs administered subcutaneously.

Although antithrombin was effective at decreasing the incidence of thromboembolic events with no additional risk of bleeding, the unexpected finding that patients receiving antithrombin had an increased rate of relapse is an issue. As this association was not constant over a number of analyses, it may well be a chance finding. However, a biological effect of antithrombin substitution on leukemia outcome cannot be completely excluded and so the use of antithrombin for thromboprophylaxis cannot be recommended until more evidence is available. Moreover, antithrombin concentrate is expensive, and substitution requires monitoring of antithrombin levels and intravenous infusion which is a burden to the patient. Therefore, while THROMBOTECT has shown that both antithrombin and LMWH are effective at preventing thromboembolic events, there remain challenges with these choices for thromboprophylaxis.

The authors of the paper conclude that the THROMBOTECT results provide the rationale to develop new studies to further determine best practice in preventing thromboembolic events in pediatric ALL. An ongoing clinical trial, the PREVAPIX-ALL (NCT02369653) study is a randomized controlled trial determining the efficacy and safety of primary prophylaxis with apixaban in prevention of thromboembolic events in pediatric patients with ALL/lymphoblastic lymphoma during induction chemotherapy. A total of 500 participants are randomized to apixaban (intervention) or no systemic anticoagulation (control). Subjects are followed for symptomatic thromboembolic events and all patients are screened for thromboembolism by ultrasound and echocardiography at the end of the induction phase. Apixaban is a direct oral anticoagulant and has been shown in adults to require no monitoring, making it an attractive option in children. The importance of availability of an oral anticoagulant is underscored by the results of THROMBOTECT with respect to the limited acceptance of subcutaneously injected LMWH. While the PREVAPIX-ALL study is open label, bias is minimized by the screening of all participants at the end of the study using standardized imaging tests and a blinded central adjudication committee.

In conclusion, THROMBOTECT has established a positive benefit-risk balance for primary thromboprophylaxis in children with ALL. PREVAPIX-ALL will add to these findings by assessing the efficacy and safety of a direct oral anticoagulant in this population. These studies will determine the optimum clinical approach for the prevention of thromboembolic events in pediatric ALL, and provide the basis for further studies of thromboprophylaxis in children in other settings.

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