BRIDGE: Bridging Warfarin With LMWH Increases Bleeding in Patients With AF

Written by Emma Hitt Nichols, PhD

Bridging warfarin interruption with low molecular weight heparin (LMWH) around the time of surgery or invasive procedures in patients with atrial fibrillation (AF) resulted in similar rates of arterial thromboembolism but significantly greater rates of minor and major bleeding. Thomas L. Ortel, MD, PhD, Duke University Medical Center, Durham, North Carolina, USA, presented data from the BRIDGE trial [Douketis JD et al. *N Engl J Med*. 2015].

It is uncertain whether bridging with LMWH is optimal practice to reduce the risk of thromboembolism during the perioperative interruption of warfarin. The purpose of the BRIDGE trial was to determine the safety and efficacy of bridging with LMWH in patients with AF who required interruption of warfarin for surgery or an invasive procedure. The investigators hypothesized that a strategy of foregoing bridging would be noninferior to bridging for the prevention of arterial thromboembolism and would be superior to bridging for major bleeding.

The double-blind, phase 3 BRIDGE trial randomly assigned 1884 patients with AF to receive bridging with LMWH or matched placebo 3 days prior to and for 5 to 10 days after surgery or a procedure. Warfarin was stopped 5 days prior to the surgery or procedure and was restarted within 24 hours afterward. The study drug was stopped when patients achieved a therapeutic INR. Patients were followed for 30 days after the initial surgery or procedure. The primary outcomes were arterial thromboembolism or major bleeding. The secondary outcomes were acute myocardial infarction, venous thromboembolism, or death, and minor bleeding.

All patients had nonvalvular or valvular AF or atrial flutter, were receiving warfarin for ≥ 3 months with a target INR of 2.0 to 3.0, and had a $CHADS_2$ score of ≥ 1. Exclusion criteria included presence of a mechanical heart valve, major bleeding within the past 6 weeks, venous thromboembolism within the past 12 weeks, creatinine clearance < 30 mL/min, and platelet count $< 100 \times 10^3/m^3$, as well as a stroke, systemic embolism, or transient ischemic attack (TIA) within the past 12 weeks or planned cardiac, intracranial, or intraspinal surgery.

The mean age was 71.7 years and the mean $CHADS_2$ score was 2.35, with about 23%, 39%, 24%, and 11% of patients having a score of 1, 2, 3, or 4, respectively. At baseline, the mean INR was 2.4, about 87% of patients had hypertension, about 31% had chronic heart failure or left ventricular dysfunction, 41% had diabetes mellitus, 8% had a history of TIA, and 16% had mitral valve disease.

Bridging with LMWH was noninferior, but not superior, to no bridging ($P_{Noninferiority} = .01$). However, there was significantly more major bleeding in the bridging arm (3.2%) compared with the no-bridging arm (1.3%; $P_{Superiority} = .005$). In addition, minor bleeding was also significantly greater with LMWH bridging (20.9%) compared with no bridging (12.0%; $P_{Superiority} < .001$). There was no significant difference among the other secondary outcomes.

Dr Ortel commented that the study was limited by the low mean $CHADS_2$ score and that most patients underwent low-risk procedures. In addition, he stated that these results are not applicable to patients who are receiving a nonwarfarin oral anticoagulant instead of warfarin.

Recombinant Human Coagulation Factor IX Fc Fusion Protein Effective in Kids B-LONG Study

Written by Muriel Cunningham

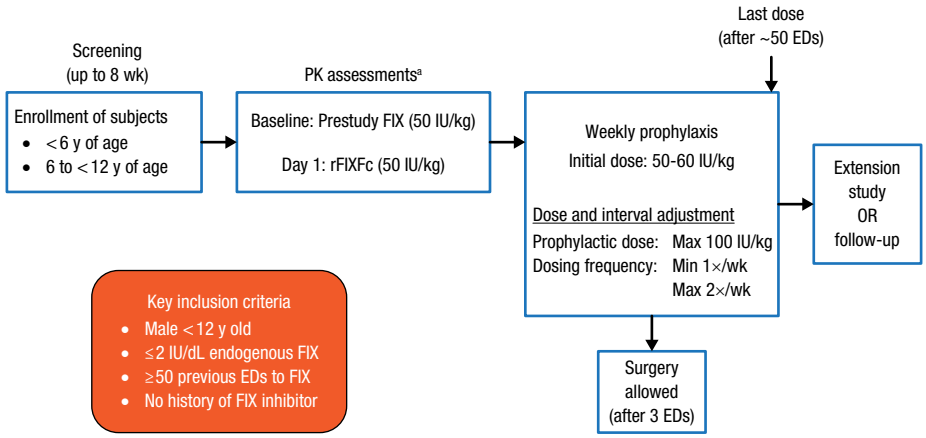
The Kids B-LONG study [NCT01440946] was conducted to evaluate the pharmacokinetics, safety, and efficacy of recombinant human coagulation factor IX Fc fusion protein (rFIXFc) in previously treated pediatric subjects with hemophilia B. Kathelijn Fischer, MD, PhD, University Medical Center Utrecht, Utrecht, The Netherlands, provided a summary of the Kids B-LONG study results.

Eligible subjects were boys aged < 12 years with ≤ 2 IU/dL endogenous factor IX (FIX) and with ≥ 50 previous exposure days (EDs) to FIX without a history of FIX inhibitor. The study schematic is illustrated in Figure 1. All subjects had pharmacokinetic assessment with FIX 50 IU/kg and then with rFIXc 50 IU/kg before this study. Then, all received weekly prophylaxis with rFIXFc and were followed for 50 EDs. Surgery was allowed after 3 EDs.

Thirty subjects were enrolled in the study; 15 patients were < 6 years old, and 15 were between 6 and 12 years. All subjects were treated with FIX prophylaxis before entering the study, and 77% were receiving FIX ≥ 2 times per week. Twenty-seven subjects (90%) completed the study, with a median study duration of 49.4 weeks. A total of 24 subjects (80%) had at least 50 EDs of rFIXFc.

Pharmacokinetic analyses indicated that rFIXFc had an increased half-life and reduced clearance in children compared with FIX products administered in the earlier phase of pharmacokinetic assessment. Also, incremental recovery with rFIXFc was similar to or slightly better than that with FIX.

Figure 1. Kids B-LONG Study Design



ED, exposure day; FIX, factor IX; PK, pharmacokinetic; rFIXFc, recombinant factor IX Fc fusion protein.

[a]A 96-hour washout period with no FIX treatment was required prior to administration of prestudy FIX, 28±7 d prior to rFIXFc dosing at baseline, and prior to administration of rFIXFc on day 1; in younger children and subjects who required a second washout attempt, a 72-hour washout period was permitted.

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No inhibitors or anti-rFIXFc antibodies developed in study subjects. The majority of subjects (86.7%) had ≥1 adverse event, the most common being nasopharyngitis (23.3%) and fall (20.0%). One mild nonserious adverse event of decreased appetite was considered to be related to study treatment; all other adverse events were considered unrelated to rFIXFc. Eleven serious adverse events occurred in 4 subjects during the study; none was considered related to the study drug. There were no discontinuations from the study because of adverse events.

No changes were made to the dosing interval in 97% of subjects. The median prophylactic dose was 59.4 IU/kg/wk (interquartile range [IQR], 53.0 to 64.8) in subjects aged <6 years and 57.8 IU/kg/wk (IQR, 51.7 to 65.0) in subjects aged 6 to <12 years.

Thirty-three percent of subjects had no bleeding episodes, and there were no joint bleeds in 63% of subjects. The overall median annualized bleeding rate was 2.0 (IQR, 0.0 to 3.1). In acute bleeding episodes, 75.0% were controlled with 1 infusion, and 91.7% were controlled with 1 or 2 infusions (median dose per infusion, 63.5 IU/kg [IQR, 48.9 to 99.4]). After the first infusions, 88.7% had an excellent or good response. Although no major surgeries were performed with rFIXFc, 3 minor surgeries were performed in 2 subjects. Excellent hemostatic response was achieved in all surgical cases. Physical activity remained the same or increased in 77% of study subjects. In her concluding remarks, Dr Fischer said she believes these data support the potential for extended-interval dosing with low bleeding rates in this population.

SOME: No Benefit With Extensive Screening for Cancer in Unprovoked VTE

Written by Emma Hitt Nichols, PhD

An extensive screening strategy for occult cancers did not provide clinical benefit over a more limited screening in patients with first unprovoked venous thromboembolism (VTE). Marc Carrier, MD, MSc, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, presented data from the SOME trial [Carrier M et al. *N Engl J Med*. 2015].

Currently, there is little consensus regarding cancer screening strategies in patients with unprovoked VTE [Carrier M et al. *Ann Intern Med*. 2008]. Some strategies are extensive, including abdominal and pelvic computed tomography (CT) imaging, whereas others are more limited and include a physical examination, routine blood testing, and a chest radiograph. The purpose of the SOME trial was to determine the efficacy of occult cancer screening with a comprehensive abdominal/pelvic CT scan in patients with unprovoked VTE.

The multicenter, open-label SOME trial randomly assigned 862 patients who presented with first unprovoked VTE to undergo limited screening or limited screening plus comprehensive CT for occult cancer, with a follow-up period of 12 months. Limited occult cancer screening was defined as basic blood work, a chest radiograph, and breast/cervical/prostate cancer screening. The comprehensive CT scan included a virtual colonoscopy and