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AVF 43

Anti-CCR2 Nanotherapeutics to Reduce Vein Wall Fibrosis Following Deep Vein Thrombosis

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Objectives: The post-thrombotic syndrome (PTS) occurs in part due to valvular reflux caused by macrophage- and fibroblast-induced vein wall fibrosis. C-C chemokine receptor type 2 (CCR2) mediates monocyte-macrophage recruitment during thrombus formation and mediates vein wall injury in murine chronic DVT settings. Here, we used a multifunctional anti-CCR2 nanoparticle to investigate the effects of anti-CCR2 (IncB) therapy in experimental murine DVT resolution and vein wall fibrosis.

Methods: Human fresh frozen plasma (FFP) clots were incubated with 0.5 U thrombin and 0.4 M $CaCl_2$ to evaluate targeting of various poly(lactic-co-glycolic acid (PLGA) fluorescent nanoparticles, with the full nanoparticle as PLGA-IncB (Anti-CCR2)-GPRP (peptide targeting fibrin)-CyAl5.5 (NIR fluorophore). Clots were washed, centrifuged, and imaged by fluorescence reflectance imaging (LICOR Odyssey, ex/em 680/780nm). Next, C57/BL6 male mice (n = 38) underwent inferior vena cava (IVC) complete ligation to develop full-stasis DVT (Fig 1, B). On day 4, mice randomly received intravenous phosphate buffered saline (PBS), PLGA-IncB-GPRP-CyAl5.5, or PLGA-IncB-CyAl5.5 (20mg/kg PLGA for nanoparticles). IVC DVT were resected on D8 to measure thrombus burden, or for Masson's trichrome (MT) and picrosirius red assessment (PSR) of thrombus and vein wall collagen, respectively.

Results: Human FFP clots showed ~6× and 3× higher binding of PLGA compounds compared with PBS control and FTP11-CyAl5, a positive control fibrin-binding peptide (Fig 1, A) ($P < .0001$). In vivo, both PLGA-GPRP-IncB and PLGA-IncB did not alter d8 thrombus burden (Fig 1, C). However, histological assessment showed reduced fibrin and erythrocytes in PLGA groups compared with PBS control (Fig 1, E). Further, d8 vein wall PSR analyses showed significantly reduced vein wall collagen in both PLGA-IncB groups (Fig 1, D; PBS vs PLGA-IncB; $P < .0001$; PBS vs PLGA-GPRP-IncB; $P = .007$), demonstrating PLGA-IncB salutary reductions on vein wall fibrosis, regardless of additional fibrin/GPRP targeting.

Conclusions: Anti-CCR2 nanotherapy significantly improves DVT resolution by reducing vein wall collagen thickness in murine DVT, without impairing thrombus resolution. This data provides a foundation for targeting CCR2 to reduce PTS.

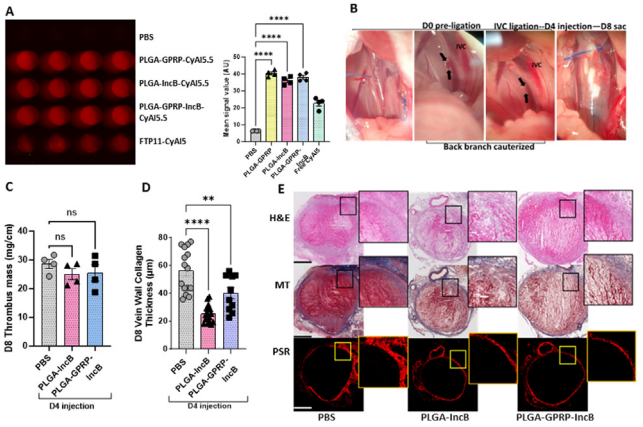

Fig. A, Poly(lactic-co-glycolic acid (PLGA) fluorescent nanoparticles binding in human plasma clots. **B-C,** Day 8 inferior vena cava (IVC) stasis thrombus analysis: thrombus weight, width, and weight/length ratio or thrombus burden showing moderate reduction in PLGA-IncB mice. **D-E,** Day 8 histological assessment of IVC thrombus and vein wall showing reduced intra-thrombus fibrin and collagen content. **D,** Shows significantly recued vein wall collagen thickness in the PLGA groups compared with phosphate-buffered saline (PBS) control groups (n = 38 mice, for thrombus burden; n = 16 for 5 mg/kg; n = 10 for 20 mg/kg; n = 12 for vein wall analysis) $^{**}P < .001$; $^{****}P < .0001$. Bars represents mean ± standard error of the mean (SEM).

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AVF 44

Acute Iliofemoral Deep Venous Thrombosis in Adolescents and Young Adults Is Unprovoked, Associated with Hypercoagulable States, and Has a High Incidence of Post-Thrombotic Syndrome

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Objectives: Acute iliofemoral deep vein thrombosis (IFDVT) in young adults and adolescents is a cause of lower extremity pain and edema that may lead to chronic debilitating symptoms. Treatment options include pharmaco/mechanical thrombectomy, stent placement, and anticoagulation. The lack of long-term data in young patients after venous stenting leads to variability in treatment with reluctance to employ stents in this population. The purpose of this study is to review the etiology, the incidence of post-thrombotic syndrome (PTS), and the role of intervention in young patients after IFDVT.

Methods: Patients presenting with acute IFDVT were identified retrospectively through Peripheral Vascular Lab databases. IFDVT was defined as any thrombus believed to be <1 month old involving the common femoral or more proximal veins. Charts were reviewed to identify demographics, risk factors for venous thrombosis, relevant laboratory data, treatment provided for the DVT, and patient outcomes.

Results: Eighty-six patients under age 25 were identified with acute IFDVT. Of these, 55 (64%) were female, 50 patients (58.1%) identified as White, 24 (28%) as Black, and eight (9.3%) as Hispanic. The primary etiology of IFDVT was found to be multisystem trauma and/or sepsis in 27 (31.4%), cancer in five (5.8%), and COVID infection in five (5.8%). None of these patients were treated with interventional therapy. The remaining 49 cases occurred in patients who were previously healthy with no specific precipitating event (unprovoked group). Of this group, 81% were female, and hypercoagulable states were identified in 25 patients (51%). Other risk factors in this group are listed in the Table. Intervention was performed in 36 (73.5%) in the provoked group, which consisted of pharmaco-mechanical thrombectomy (PMT) with balloon angioplasty in 22 patients and with stent insertion in 14. One year after IFDVT, 19 patients (43.2%) reported no PTS symptoms, 10 (22.7%) reported mild symptoms, and 15 (34.1%) reported moderate or severe symptoms. Recurrent iliofemoral DVT occurred in 18% of patients at 1 year and 26.2% at 3 years after IFDVT.

Conclusions: Acute IFDVT in young patients is most often unprovoked, typically in females, the majority of whom are found to have a hypercoagulable state. Most of this cohort were treated without venous stenting. Significant PTS and recurrent IFDVT occurred frequently after the initial

Table. Risk factors in young patients with unprovoked iliofemoral deep vein thrombosis (*IFDVT*)

Unprovoked group (n = 49) Risk factor	No. patients (%)
Defined hypercoagulable state	25 (51)
Oral birth control use at time of DVT	23 (47)
Body mass index >30 kg/m^2	17 (35)
Current tobacco use	9 (18)
Iliocaval atresia	6 (12)