venous thromboembolism cannot be endorsed for all patients with primary CNS tumors or untreated CNS metastases. After a frank discussion of the risks and benefits, it can be considered for an individual patient with additional high-risk factors, as described in my review.

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Since publication of her article, the author reports no further potential conflict of interest.

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DOI: 10.1056/NEJMc1408866

More on Platelet-Rich Plasma Injections in Acute Muscle Injury

TO THE EDITOR: Reurink et al. (June 26 issue)[1] report no benefit of intramuscular platelet-rich plasma (PRP) injections in patients with acute hamstring injuries. The delayed administration and low dosage of PRP injections in their trial may well have rendered PRP injections ineffective. Growth factors in PRP exert an antiapoptotic, chemotactic, antiinflammatory, and proliferative effect on fibroblasts, neurons, and myoblasts; some of these effects are dose-dependent and strongly influence myogenesis, angiogenesis, and fibrogenesis.[2] These events occur a few hours after muscle damage. By the time PRP injections are administered (within 5 days after the injury), many of the injured microenvironmental biologic targets of PRP have either disappeared or undergone a phenotypic shift. Three in vivo studies in which PRP treatment was initiated either a few hours or 2 days after injury showed histologic or functional improvement in the group of patients who received treatment.[3-5] The dosages in these studies[3] were at least 2.5 times as high as the dosages conveyed for each injection in the trial by Reurink et al. (insulin-like growth factor 1 [IGF-1], 225,000 pg vs. 90,000 pg, and dosage of platelet-derived growth factor [PDGF], 50,000 pg vs. 20,000 pg).

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DOI: 10.1056/NEJMc1409204

THE AUTHORS REPLY: The timing of PRP injections is subject to debate, since the environmental milieu and the effect of growth factors change over time during healing.[1] In vivo studies do not show that the optimal time window for injections is within 2 days after injury, since this has not been compared with a delayed period before administration of injections.[2] In previous clinical studies involving athletes with acute muscle injuries, the PRP was injected 2 or 3 days after inju-

ry.[3,4] We injected PRP a median of 3 days (interquartile range, 2 to 4) after injury. In a Cox regression analysis, adjustment for the time between injury and injection did not materially change the treatment effect.

We injected three 1-ml depots at each procedure. According to a recent study by Magalon et al.,[5] this total of 3 ml corresponds to a PDGF dosage of 40,000 pg (which is slightly less than the dosage reported by Anitua et al.). IGF-1 was not analyzed in their study. Magalon et al. describe dosages of other growth factors and show the content of different PRP preparation systems.[5]

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DOI: 10.1056/NEJMc1409204

Pyogenic Granuloma as a Cutaneous Adverse Effect of Vemurafenib

TO THE EDITOR: Vemurafenib has altered the prognosis of patients with metastatic melanoma with *BRAF* V600 mutations.[1] However, this agent is associated with a wide spectrum of cutaneous toxic effects, including squamous-cell carcinoma, primary melanoma, keratoacanthoma, and rashes.[2] We have identified pyogenic granuloma as a further cutaneous event associated with vemurafenib.

A 69-year-old man who had presented 2 years previously with a superficial spreading melanoma with a Breslow thickness of 1 mm was found to have bilateral axillary lymphadenopathy; a biopsy revealed melanoma with a *BRAF* V600E mutation. Staging investigations showed metastatic disease, with a 23-mm lesion in the right thalamic region, a 40-by-22-mm mass in the right axillary node, enlarged left axillary lymph nodes, and peritoneal deposits. Treatment was initiated with vemurafenib at a standard dose of 960 mg twice daily. Within 6 days, a widespread rash developed, which necessitated an interruption in treatment for 1 week and reinitiation at 75% of the initial dose (720 mg twice daily). At 12 weeks, a keratoacanthoma over the left clavicle and a rapidly enlarging vascular lesion on the left alar rim of the nose developed (Fig. 1A). Both lesions were excised, with the latter requiring grafting. Histologic analysis of the nasal lesion confirmed pyogenic granuloma (Fig. 1B). Vemurafenib was continued, but 4 weeks after excision, six further pyogenic granulomas erupted close to the nasal skin graft (Fig. 1C). Four of these lesions were curetted, and two were left in situ. At this point, 24 weeks of vemurafenib had been administered, with a complete tumor response on imaging. In view of the rapid recurrence of lesions, vemurafenib was withheld for 2 weeks, during which no further lesions erupted, and the two residual pyogenic granulomas remained static in size. On reinstitution of treatment at 50% of the full dose (480 mg twice daily), these two lesions grew very slowly (Fig. 1D).

The pattern of occurrence of pyogenic granulomas on and off treatment and the dose dependency suggest a mechanism driven by vemurafenib. Paradoxical activation of the MAPK pathway has been postulated as causing the development of squamous-cell carcinomas and keratoacanthomas in patients treated with this drug.[3] This factor, coupled with the observation that pyogenic granulomas strongly overexpress MAP kinases,[4] leads us to hypothesize that the molecular mechanisms driving dermatologic tox-