inside blood commentary

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Wei et al, page 296

Which 'roid is all the rage?

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In this issue of *Blood*, Wei and colleagues report results on the first prospective clinical trial to compare high-dose dexamethasone to prednisone for the initial treatment of immune thrombocytopenia (ITP).[1]

In 1951, William Harrington and colleagues demonstrated that a substance in the blood of ITP patients was destroying platelets, suggesting that the thrombocytopenia reflected shortened platelet survival rather than decreased platelet production by the bone marrow.[2] After the autoimmune nature of ITP was further described in the 1960s, corticosteroids became the traditional first-line treatment and were combined with other immunosuppressants in varying combinations and dosages.[3] Which steroid should be the preferred agent, however, remained a topic of debate. Similar to other autoimmune conditions, high-dose oral prednisone has been used for decades in most patients, with a prolonged taper after an adequate response is achieved. This regimen has drawbacks, in that many patients do not tolerate high-dose steroids for the weeks to months of therapy that are often required to ensure adequate platelet counts to reduce bleeding.

In 1994, Judith Andersen showed that pulsed dexamethasone was an effective agent for refractory ITP when given every 28 days for 6 cycles. Many of these patients had been treated with multiple lines of therapy including prednisone.[4] This finding was followed in 2003 by a study demonstrating the efficacy of a single cycle of pulsed dexamethasone in treatment-naïve patients; however, there was no comparison with prednisone in that study.[5] A third study in 2007 reported a larger cohort of patients treated with pulsed dexamethasone, dosed either every 14 days for 4 cycles or every 28 days for 6 cycles. That study demonstrated excellent response, with >80% of patients achieving continued remission at 15 months; this study, too, has been faulted for not having included prednisone in a comparator arm.[6] In fact, until now, dexamethasone has never been directly compared with prednisone in a randomized fashion.

In their study, Wei and colleagues[1] randomized treatment-naïve patients to receive either oral dexamethasone at a dose of 40 mg daily for 4 days or to receive standard prednisone dosing with a taper. Patients in the dexamethasone arm who did not respond to the initial course were given a second pulse starting on day 10 if they failed to achieve a platelet count $>30 \times 10^9$/L or if they had bleeding symptoms.

Patients in the high-dose dexamethasone arm, as compared with the prednisone arm, had a higher overall response (82.1% vs 69.1%; $P = .044$) and a shorter median time to response (3 days vs 6 days; $P < .001$); and a higher percentage of them had a complete response (50.5% vs 26.8%; $P < .001$). There was no difference between treatment arms, however, in sustained response (40% vs 41.2%; $P = .884$) or in sustained complete response (27.4% vs 17.5%; $P = .120$). Most patients in the prednisone arm (60.8%) received treatment for 1 to 3 months, and the overall median duration of treatment was 11 weeks. Given the shorter time of steroid exposure, there were fewer adverse events in the dexamethasone arm. Approximately 13% of patients in the prednisone arm developed a cushingoid appearance and 10% experienced weight gain, whereas none of the patients in the dexamethasone arm experienced these complications.

The lingering and most important question is whether repeated cycles of pulsed dexamethasone would be superior to prednisone in yielding long-term responses. To answer this question, one must eagerly await a future study comparing repeated cycles of dexamethasone every 14 or 28 days as the comparator arm to prednisone in an attempt to induce long-term remission.

In recent years, dexamethasone has gained growing support for its use in the up-front treatment of ITP. By demonstrating that dexamethasone is as efficacious as prednisone, and has a more favorable side-effect profile for treatment-naïve patients, Wei and colleagues show us which 'roid should be all the rage.

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