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Off-Label Drug Uses

Dexamethasone: Idiopathic Thrombocytopenic Purpura in Children and Adolescents

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts,* a quarterly publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@kumc.edu.

BACKGROUND

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenia, is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood count less than 100 x 10^9/L) without evident cause. Historically, it was thought that increased platelet destruction was related to autoimmune processes. However, the cause is now considered to be due to impaired platelet production as well as autoimmune effects. ITP may be classified by duration: newly diagnosed, persistent (3 to 12 months duration), or chronic (at least 12 months duration). Because the majority of children with newly diagnosed ITP often do not have significant bleeding, most cases may be managed with observation. Therapy directed at increasing platelet counts is based on the recommendation of the hematologist. All children with severe bleeding should be treated, and therapy should be considered for pediatric patients with moderate bleeding or those at increased risk of bleeding. Though dexamethasone is US Food and Drug Administration (FDA)–approved for ITP in adults and is considered first-line therapy in this population, dexamethasone treatment of ITP in children is considered off-label.[1]

PATIENT POPULATION

Children and adolescents (age range, 3 to 17 years) with persistent or chronic refractory ITP.

DOSAGE AND DURATION

Oral

Guidelines have provided varied oral dosage regimens for dexamethasone in the management of ITP, including 28 to 40 mg/m^2/day, without specifying duration or cyclic high-dose regimens (0.6 mg/kg/day for 4 days every 4 weeks for 6 cycles).[1,2]

Small prospective trials have documented oral dosage regimens as 20 mg/m^2 daily (in 2 divided doses) for 4 days every 4 weeks for a total of 6 cycles/courses[3] or 0.6 mg/kg daily for 4 consecutive days once a month for 6 courses.[4]

Intravenous

Administered as 20 mg/m^2 daily for 4 days. A cycle was administered every 15 days for a total of 4 courses.[5]

RESULTS

Dexamethasone in the management of refractory or relapsed ITP has been primarily evaluated in noncontrolled settings enrolling fewer than 100 patients, demonstrating varied benefit ranging from 25% to 84% of treated patients.[3-5]

In guidelines, high-dose dexamethasone is recommended as second-line therapy in children and adolescents with unresponsive ITP.[1,2]

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Guidelines

American Society of Hematology

In the American Society of Hematology (ASH) evidence-based practice guidelines, initial (first-line) pharmacological management of pediatric ITP is recommended as a single dose of intravenous immunoglobulin (IVIG) or a short course of corticosteroids. IVIG is recommended if a more rapid increase in platelet count is needed. Anti-D therapy is considered first-line in Rh-positive, nonsplenectomizecd children.

In children with chronic or persistent ITP that is refractory to initial therapy, appropriate second-line therapy is recommended as rituximab or high-dose dexamethasone for those with significant bleeding despite initial therapy, as an alternative to splenectomy, or as therapy in patients who did not respond favorably to splenectomy. Oral doses of dexamethasone reviewed in these guidelines include 6 cycles of the drug with a cycle defined as 0.6 mg/kg/day for 4 days every 4 weeks.

Single or combination regimens that do not have sufficient data for specific recommendations include azathioprine, danazol, interferon, mycophenolate mofetil, cyclosporine, anti-CD52 antibody, and thrombopoietin receptor antagonists. The possible exception to this list is dapsone, which demonstrated a 66% response rate in a small retrospective review.[2]

International Consensus Report

In a consensus report on the management of primary ITP, first-line initial therapy in pediatric patients is defined as IVIG or IV anti-D immune globulin in patients with severe bleeding. Prednisone or prednisolone may be effective in children; however, because of the serious adverse effects associated with prolonged steroid therapy in children, these drugs are reserved for short-term therapy only.

In pediatric patients with persistent or chronic ITP who have not responded to initial therapy, treatment options may include dexamethasone, high-dose methylprednisolone, or rituximab (evidence levels IIa to IIb). As noted, adverse effects with steroids (eg, sleeplessness, behavioral changes, hypertension, anxiety, etc) may limit the usefulness of these regimens. The guidelines note that dexamethasone doses have ranged from 28 to 40 mg/m^2/day in reviewed studies with a response rate up to 80%. The approximate time to response is typically 3 days, but the responses are of short duration unless cycles are repeated.

Some single or combination regimens that are beneficial in adults do not have enough adequate data to support their use in children. The guidelines state that no recommendations can be made for use of cyclosporine A, azathioprine, vinca alkaloids, prolonged prednisone, IVIG, anti-D immune globulin, and/or danazol in children with chronic or persistent ITP.[1]

Controlled Trials

In a 2:1 randomized but unblinded study of 23 children with chronic ITP, 15 received oral dexamethasone (0.6 mg/kg daily) for 4 consecutive days once a month for 6 courses and the remaining 8 received a single IVIG dose (800 mg/kg) once a month for 6 months. If the platelet count was less than 30 x 10^9/L on the third day, another IVIG dose was administered. After 4 courses of either therapy, nonresponders were offered the alternate therapy. A total of 20 patients received dexamethasone, including 5 IVIG nonresponders, with a total of 14 patients receiving all 6 courses. A total of 11 patients received IVIG, including 3 dexamethasone nonresponders, with only 5 patients completing all 6 courses. Long-term response, defined as either partial (at least 30 x 10^9/L platelet count and increase from baseline) or complete (increase in platelet count of at least 150 x 10^9/L during at least 3 months without therapy), was 25% (5/20) and 9% (1/11) in the dexamethasone and IVIG groups, respectively (P = .38) Short-term response (platelet count at least 30 x 10^9/L on day 3 of first treatment cycle) occurred in 75% (9/12) of the dexamethasone group and all patients with available data in the IVIG group. At a 5-year follow-up, 3 of the 5 responders to dexamethasone and the 1 responder to IVIG were still in remission.[4]

Noncontrolled Trials

In a prospective 10-month open trial, 13 children (median age, 8 years; range, 3 to 16 years) with chronic, refractory ITP (more than 6 months duration) received intravenous dexamethasone (20 mg/m^2) daily for 4 days every 15 days for 4 cycles. Response was based on changes in platelet counts and defined as complete (greater than 150 x 10^3/mm^3), moderate (between 50 and 150 x 10^3/mm^3), minimal (between 20 and 50 x 10^3/mm^3), and no response (less than 20 x 10^3/mm^3). One patient was lost to follow-up. Of the remaining 12 patients, response was complete (66.6%), moderate (17%), or none (17%). Four patients responded after the second cycle, 2 after the third cycle, and the remaining 4 after the fourth cycle. Median duration of response was 5 months (range, 3 to 11 months).[5]

In an open prospective trial, 17 patients (median age, 10 years; age range, 4 to 17 years) with ITP

received oral dexamethasone (20 mg/m^2 in 2 divided doses daily) for 4 days every 4 weeks for a total of 6 cycles/courses. At baseline, all patients had platelet counts less than 20 x 10^9/L and exhibited severe bruising, petechiae, and/or epistaxis. At 1 month post therapy, 6 (35%) patients had platelet counts within normal range, of whom 5 (29% of the total) maintained at follow-up of 1 year post therapy. In 6 other patients, the platelet count increased at the end of each of the 6 courses, but rapidly returned to baseline. Five patients discontinued treatment due to a lack of benefit: 1 at the end of the fourth course and 4 at the end of the fifth course. Onset of response was observed at 5 days after the beginning of therapy to the start of the fourth course.[3]

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Guidelines have noted that adverse effects with steroids (eg, sleeplessness, behavioral changes, hypertension, anxiety, etc) may limit the usefulness of these regimens in children.[1]

In the reviewed data, side effects with steroids have included hypertension requiring antihypertensive therapy, fatigue, irritability, anxiety, moodiness, aggressiveness, altered mental state, depressive feelings, concentration difficulties, hyperactivity, abdominal pain, striae, hirsutism, acne, sleeping disturbances, increased appetite, dyspepsia, headache, facial flush, signs of Cushing syndrome, myalgia, fever, and weight gain.[3-5] In one study, most side effects appeared in the first treatment cycle.[4]

THERAPY CONSIDERATIONS

Dexamethasone in the management of refractory or relapsed ITP has been primarily evaluated in noncontrolled settings demonstrating varied benefit in treated patients. In guidelines, high-dose dexamethasone is recommended as second-line therapy in children and adolescents with unresponsive ITP.

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