Refractory Kawasaki Disease

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Kawasaki disease (KD) is a vasculitis of early childhood with a striking predilection for the coronary arteries. Treatment is directed toward the inflammatory response responsible for clinical and pathologic manifestations. Current treatment reduces risk of coronary sequelae at 1–2 months after disease onset from 20–25% to 2–4%.[1] When given within 10 days of onset of fever, intravenous immunoglobulin (IVIG) at 2 g/kg with high dose aspirin (80–100 mg/kg/day) results in rapid defervescence and clinical improvement in ~90% of patients.

Specific guidelines do not exist for the management of patients who do not respond with defervescence and subsidence of inflammatory changes to IVIG (2 g/kg) with aspirin. These nonresponsive or refractory patients are a challenge because the risk for coronary artery sequelae increases with prolonged fever. It is not possible to predict prospectively that a KD patient will not respond to initial therapy; responders and nonresponders have comparable baseline characteristics, such as age, sex and number of diagnostic criteria. Some have identified lab predictors of IVIG nonresponsiveness, such as degree of anemia, height of C-reactive protein and lactate dehydrogenase elevation,[2] but others found no significant lab differences between responders and nonresponders.[3,4] A retrospective study found that KD patients treated earlier in their illness were more likely to be refractory to therapy[3]; other studies did not replicate this finding.[5]

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INITIAL APPROACH TO THE REFRACTORY KD PATIENT

Few studies address treatment of IVIG-refractory KD because only 10–15% of patients fail initial therapy, and the disease is self-limited, making it difficult to ascribe benefit to a therapeutic intervention without controlled trials with adequate numbers of patients. Such studies do not exist.

Most centers, including ours, treat the KD patient who remains febrile or has recurrence of fever 48–72 h after initial 2 g/kg IVIG and high dose aspirin with an additional 2 g/kg IVIG.[5] In a retrospective study of 179 patients treated with IVIG, 89% responded to the first dose of IVIG, and 67% of nonresponders responded to a second dose of IVIG.[3] Thus, only 3–4% of KD patients failed to respond after the second dose of IVIG with aspirin. Although most US centers use a second IVIG dose of 2 g/kg, no controlled trials have compared 1 g/kg to 2 g/kg IVIG for retreatment. The antiinflammatory effect of aspirin also may be optimized by monitoring serum salicylate levels. Judicious adjustment of salicylate dose to 120 mg/kg/day or more, with monitoring of serum salicylate concentration to detect impending toxicity, may be helpful. When treating apparently refractory KD patients, it is also prudent to reconsider the diagnosis, as no diagnostic test exists for KD and other illnesses may mimic its presentation.

There are various approaches to the KD patient who remains febrile and ill after 2 doses of 2 g/kg IVIG, and there are very few data on which to base recommendations. The most common approaches are to treat (1) with a third dose of IVIG (usually 2 g/kg) or (2) with corticosteroids. We most often give a third dose of IVIG, although at least some patients who have failed 2 doses of IVIG also fail the third. In the previously cited study, only 2 of 179 patients received a third dose of IVIG, and both remained febrile.[3] An alternative is to treat KD patients who fail 1, 2 or 3 doses of IVIG with corticosteroids as "rescue therapy."

STEROID USE IN KD

Although KD is a vasculitis and corticosteroids are a mainstay of therapy for vasculitides, KD is unusual in that there is strong evidence of an infectious etiology. Reluctance to use corticosteroids for KD dates to Kato's[6] study in 1979, in the pre-IVIG era. In this small study KD patients treated with oral prednisolone had a particularly high rate of development of coronary aneurysms (11/17, 65%). None of 7 patients in this study treated with aspirin and prednisolone developed coronary aneurysms. Although this and other early studies led to caution regarding steroids in KD, it was a small, nonrandomized study, and steroids were used as "primary therapy." Recent reports of corticosteroids as "rescue therapy" in IVIG-refractory KD have not shown an association between corticosteroids and an increase in coronary aneurysms. However, caution must still be exercised, because possible adverse effects of corticosteroids include hypertension and thrombosis.

KD patients refractory to IVIG were reported to improve and to defervesce after steroid therapy in several small series. In 1996 Wright reported 4 children who had failed 2 doses of IVIG (2 g/kg followed by 1 g/kg) and who improved after intravenous 30-mg/kg/day methylprednisolone pulses for 1–3

days without significant worsening of coronary abnormalities (all had abnormal coronary arteries preceding the steroid doses).[7] In 2000 Dale reported 7 KD patients who remained febrile despite IVIG and aspirin and were then treated with oral prednisolone (2 mg/kg/day) for 2 weeks followed by a 6-week taper.[8] Six of 7 patients became afebrile within 72 h of steroids (5 within 48 h), and in none of these 6 patients did coronary disease progress. One patient remained febrile for 10 days despite steroids, with progression of coronary abnormalities. In a small study Hashino treated 17 patients who were febrile despite aspirin and 2 IVIG courses (2 g/kg followed by 1 g/kg), with either pulsed steroids (9) or additional IVIG (8).[9] The 9 who received steroids improved; however, immediate but transient coronary dilatation was noted in 3/9 after steroid therapy. These reports suggest that corticosteroids often hasten defervescence in IVIG-refractory patients. However, a multicenter trial clearly is needed to assess the relative risks and benefits of steroids, especially on coronary abnormalities, and to determine the most appropriate route of administration and dose.

OTHER THERAPIES

Even less published experience exists in IVIG-refractory KD for the use of other therapies typically used to treat of other vasculitides. Two KD patients were treated with cyclophosphamide after continued fever and other signs of inflammation despite 2 courses of 2 g/kg of IVIG and 2–4 3-day courses of intravenous methylprednisolone (30 mg/kg/day).[4] Both experienced return of inflammation when corticosteroids were tapered. The addition of cyclophosphamide to prednisone appeared to be associated with resolution of symptoms and lab abnormalities, and both medications were tapered slowly over 1.5 and 7 months.

In a recent Japanese study, 50 refractory KD patients improved after plasma exchange, and coronary abnormalities were detected in 20%; 69 refractory patients were treated with additional IVIG, and coronary abnormalities were detected in 41%.[10] Cyclosporin A was used in a highly refractory patient, who had failed 4 courses of IVIG and 3 days of pulse steroids.[11] The patient finally became afebrile 7 days after addition of cyclosporin A to steroids, although coronary aneurysms remained. Although these therapies apparently have adverse effects, the number of patients treated is extremely limited, and the necessary controlled trials have not been performed. That KD is self-limited compounds the difficulty of reaching conclusions regarding efficacy of a specific therapy without a controlled trial.

Ulinastatin is a neutrophil-elastase inhibitor available in Japan that is purified from human urine and used in Japan for inflammatory conditions such as Stevens-Johnson syndrome [12] and for refractory KD in small uncontrolled trials.[13] Additional studies are needed with appropriate controls.

Recently infliximab (Remicade), a monoclonal antibody against tumor necrosis factor-α (TNF-α), was used in a few IVIG-refractory KD patients. Infliximab is licensed for treatment of rheumatoid arthritis and Crohn's disease. It is hypothesized to be beneficial in KD because TNF-α may be involved in the inflammatory process in acute KD.[14] Burns et al.[15] reported 7 acute KD patients who were refractory to IVIG and aspirin and then treated with 1 infusion of 5 mg/kg infliximab. These patients had failed to respond to 2 or 3 doses of IVIG, and 3 remained febrile despite 3–5 doses of methylprednisolone. All improved and defervesced after one dose of infliximab with no adverse effects. Coronary aneurysms were noted in all 7 patients before infliximab therapy, with subsequent normalization in 3/7 patients. Our experience with infliximab for refractory KD is limited to 2 patients, one who had an 8-day response but then relapsed and another in whom the response was indeterminant. To address the benefit of infliximab in refractory patients, a multicenter clinical trial is planned.

CONCLUSIONS

Therapy for KD with IVIG and aspirin has reduced the incidence of coronary aneurysms remarkably, from about 20–25% to <5%. However, for nonresponding patients, limited data are available to guide therapy. Although most opt to treat such patients with additional IVIG, some patients remain refractory to therapy and are treated with corticosteroids and occasionally more experimental therapies such as immunosuppressants (e.g. cyclophosphamide) or infliximab. The relative value of these rescue therapies is difficult to assess due to both the self-limited nature of KD and the limited number of patients. Multicenter trials are necessary to assess clinical response[5] and potential adverse outcomes. Because no diagnostic test exists for KD, one must always remember to remain vigilant for the possibility of an alternative diagnosis in the patient with apparent refractory KD.

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