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Changing Management of Kawasaki Disease

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Kawasaki disease (KD) is an acute, self-limiting inflammatory disorder of unknown etiology, characterized by vasculitis affecting predominantly medium-size arteries, particularly the coronaries (1). The diagnosis of KD is based on the occurrence of fever, persisting at least five days, associated with constellation of nonspecific clinical features and evidence of systemic inflammation. Complete KD is confirmed in presence of four out of five typical signs (changes in extremities, polymorphous exanthem, bilateral bulbar conjunctival injection without exudate, changes in lips and oral cavity, and cervical lymphadenopathy, usually unilateral). These classic signs are rarely present simultaneously at the time of first observation, but can appear subsequently, possibly delaying the diagnosis. Moreover, the suspect of KD may increase in presence of several other "nonclassic" clinical findings such as irritability, which is nearly always present, although not included in the diagnostic criteria (1, 2). A significant percentage of children (15-36.2% depending on the study) may present an incomplete form of the disease. According to the algorithm proposed by the American Heart Association (AHA), incomplete KD should be considered in all children with unexplained fever for ≥ five days, associated with two or three of the principal clinical features of KD (1). Incomplete KD is at risk of heart complications as the classical form; therefore, it is now accepted that KD can be considered as a continuous spectrum, ranging from incomplete to complete forms (2). KD causes coronary artery aneurysms (CAA) in 15-25% of untreated patients and is also potentially an important cause of long-term cardiac disease in adulthood (1, 3).

As stated by AHA in 2004, combined administration of intravenous immunoglobulin (IVIG) (2 g/kg administered slowly in a single infusion) and aspirin at a high dose (80-100 mg/kg/day in four doses) is effective in reducing the risk of CAA. Up to 20% of patients may show IVIG resistance with consequent increased risk of developing CAA, unless they receive additional treatments (3). Several scoring systems have been proposed to identity children at higher risk of IVIG resistance, i.e. Kobayashi, Egami and Sano scores (4). These scores have been developed in Japanese children and when tested in American patients they showed good specificity, but low sensitivity (4). A negative score in a non-Japanese child does not reliably exclude an increased risk of IVIG resistance and CAA development (3). Moreover, the recently published Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki disease (RAISE study) showed that Japanese patients at high risk of IVIG resistance (Kobayashi score ≥ 5) and treated with IVIG plus aspirin had a coronary artery abnormalities complication rate of 23%, reinforcing the importance of an early recognition of children at risk of IVIG resistance (5). Indeed, children with severe form of KD could benefit from additional anti-inflammatory therapy to reduce the risk of CAA. During the last years, some studies evaluated the usefulness of administering corticosteroids in adjunct to IVIG and aspirin for the primary treatment of severe KD. A recent meta-analysis of nine clinical studies involving 1011 patients showed that administration of corticosteroids plus IVIG significantly reduced the risk of coronary abnormalities; similar results were also observed in subgroup analyses of randomized controlled studies (number = 6) and studies enrolling only patients with a high risk of IVIG resistance (number = 3) (6). Moreover, corticosteroids administration was not associated with increased incidence of severe adverse events (6). Despite these intriguing results, the meta-analysis did not exactly clarify whether all children with KD (particularly non-Japanese ones) should be treated with steroids and which was the preferred regimen (type of steroid, route of administration, dose, duration).

Taking into account these recent studies, updated guidelines have been recently proposed for management of KD in the UK (3). UK guideline confirms that IVIG should be administrated in a single-dose at 2 g/kg and suggests aspirin administration during the acute phase of the disease at lower doses (30-50 mg/kg/day). As previously recom-

mended, the anti-inflammatory dose should be reduced to an antiplatelet dose of 3-5 mg/kg/day once fever and inflammation subsided (3). UK guideline is particularly innovative compared with those of AHA because for the first time it proposes corticosteroids administration for the primary treatment of severe KD (3). The authors suggest that corticosteroids should be considered in:

1) IVIG-resistant patients

2) Children with features of severe disease (< 1 year old; those with markers of severe inflammation, including persistently elevated C-reactive protein (CRP) despite IVIG, liver dysfunction, hypoalbuminemia, and anaemia)

3) Children who develop features of hemophagocytic lymphohistiocytosis and/or shock

4) Patients who already have evolving coronary and/or peripheral aneurysms with ongoing inflammation at presentation

5) Kobayashi risk score ≥ 5

In the absence of robust evidence, UK guideline provides two suggested regimens:

1) Intravenous preparation equivalent to 2 mg/kg prednisolone (i.e. methylprednisolone 0.8 mg/kg twice daily) for 5-7 days or until CRP normalizes, followed by oral prednisolone 2 mg/kg/day, weaning over the next 2-3 weeks

2) Methylprednisolone 10-30 mg/kg intravenous (IV) once a day for three days, followed by oral prednisolone 2 mg/kg/day until day seven or until CRP normalizes, weaning over the next 2-3 weeks.

AHA and UK guidelines also differ regarding the evaluation of cardiac complications of KD. AHA guidelines reported that perivascular brightness, ectasia, and lack of tapering of the coronary arteries in the acute stage of KD may represent coronary arteritis before the formation of aneurysms (1). UK guideline reinforces this assumption emphasizing that an echocardiographic evaluation performed in the first week of KD may already show vessel abnormality, including brightness (suggesting inflammation) or dilatation, and/or extra coronary manifestations, including mitral regurgitation and pericardial effusion. Patients with these features may also be at greater risk of CAA, and therefore, may require corticosteroids (3). UK guideline recommends a minimum of three echocardiograms in the first six weeks of the illness: at the diagnosis, 6-8 weeks after the onset of the disease, and an intermediate echocardiogram at 10-14 days of the disease onset if the initial echo was normal and the disease activity was arrested (3).

Finally, unlike AHA guidelines, UK guidelines suggest a role for anti-tumor necrosis factor-α (TNF-α) therapy for the treatment of refractory KD. Particularly, the administration of infliximab (a chimeric murine/human IgG1 monoclonal antibody specifically binding TNF-α) has been proposed for patients with IVIG resistance (6 mg/kg IV, 1-2 doses) (3). Etanercept (a soluble TNF-α receptor) has been also proposed as an adjunctive therapy for KD (7). Other immunosuppressive agents such as ciclosporin, cyclophosphamide, methotrexate, and plasma exchange, have occasionally been used to treat patients who do not respond to IVIG, steroids and anti-TNF-α; but to date, the use of these agents has not been routinely recommended (3).

Recently, two studies evaluated the clinical and biochemical characteristics of KD in Iranian children (8, 9). Soleimani et al. reported a significant prevalence of liver abnormalities (46.8%), ranging from mild asymptomatic increase in the liver enzymes to severe cholestatic hepatitis (8). In patients presenting with febrile cholestatic jaundice, a high index of suspicion to KD should always be maintained (10). Soleimani et al. also reported hydrops of gallbladder in 12.7% of the enrolled patients (8). Abnormal gallbladder findings were significantly more frequent in children who developed CAA (11); but, further studies are needed to clarify whether patients with hydrops of gallbladder may require a more aggressive therapy, for example corticosteroids.

Sedighi et al. reported a high percentage of coronary artery abnormalities (17/74, 22.9%) in Iranian children affected by KD, particularly in the incomplete cases (11/30, 36.7% vs. 6/44, 13.6% in complete forms, P = 0.028). Moreover, among the 72 patients promptly treated with IVIG, a high percentage of children (11/72, 15.3%) developed CAA, even if only 12.1% of cases showed IVIG resistance (9). The authors reported that the relatively higher prevalence of incomplete KD could explain these results, but emphasized that the golden time for IVIG administration should be revised and possibly decreased to reduce the occurrence of heart complication in children living in the area of Hamedan, considered as a high-prevalence area for KD (9).

Management of KD is still of particular concern for pediatricians. However, recent advances have been important in improving the prompt disease diagnosis as well as developing a more effective treatment for KD. Identification of patients at increased risk of IVIG resistance and consequentially of acute and long-term heart complications is a goal for the future. Novel clinical scores should be proposed to identify non-Japanese children at the highest risk of CAA who may benefit from addition of corticosteroids and/or anti-TNF in the primary treatment. Finally, stronger evidence is needed to definitively clarify the patient selection, dose, route of administration, and safety of corticosteroids and/or other anti-inflammatory agents.

Authors' Contributions

Francesco Vierucci wrote the manuscript; Andrea Azzarelli, Rossana Gualtierotti and Raffaele Domenici critically revised the manuscript for important intellectual content.

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