

Update in pediatric rheumatology

R. Cimaz

Clinica Pediatrica. Fondazione Policlinico Mangiagalli, Milano Italy. Università Lyon 1. Lyon. France.

In recent decades many advances in paediatric rheumatology have been achieved, in particular in classification, outcome measurements, and therapeutic regimens. In particular, the collaborative effort of multicenter studies has helped to improve the recognition and treatment of less common rheumatic diseases in childhood. Due to a close cooperation among researchers in Europe and United States, new drugs and treatment strategies have been tried in a large number of children, with a significant amelioration of the quality of life. Nevertheless, connective tissue diseases remain a challenge for paediatric rheumatologists over the world. This review will briefly focus on some recent advances the field of pediatric rheumatology. For space constraint, we have chosen to cite those articles that seemed to us more important, either from a research or from a clinical point of view, and we have concentrated our attention on juvenile idiopathic arthritis and the major connective tissue diseases (systemic lupus, dermatomyositis, and Kawasaki disease).

JUVENILE IDIOPATHIC ARTHRITIS

The International League of Associations for Rheumatology met in 2001 to delineate, for research and clinical purposes, relatively homogenous, mutually exclusive categories of idiopathic arthritis in childhood, based on predominant clinical and laboratory features¹. Juvenile idiopathic arthritis (JIA) is now the preferred term, and the classification was recently approved for use in trials by the US Food and Drug Administration.

Among diagnostic techniques, MRI was recently studied by Knight et al², who examined MRI T2 relaxation times in the weight-bearing cartilage of the distal femur in healthy children and in children with JIA. Differences in cartilage microstructure were seen; this may allow for early detection of cartilage changes and provide an objective and quantitative method of monitoring disease progression, with the long-term potential to guide therapy.

The issue of low bone density on children with rheumatic disorders, including JIA, is becoming more and more important in the follow-up of our patients. While dual-Xray absorptiometry (DXA) is still the gold standard to monitor bone density, new promising approaches such as bone ultrasound are gaining interest^{3,4}. Peripheral quantitative Computer Tomography, for the time being still a research tool, has been used to evaluate bone density and geometric parameters in the forearm of 57 patients with polyarticular, oligoarticular, and systemic JIA⁵. Patients in all disease groups had significantly reduced muscle cross-sectional area, which strongly correlated with muscle force and abnormalities in geometric parameters of bone, including a significant reduction in cortical thickness. Trabecular density was affected only in the polyarticular JIA group, and cortical density was normal in all subgroups. Thinned bony cortices might therefore predispose to fractures even though cortical bone density itself is normal.

Treatment of JIA is still based on administration of nonsteroidal anti-inflammatory drugs, with the addition of second-line drugs in case of insufficient response. Among the numerous second-line drugs now available, methotrexate (MTX) is still the first choice in patients with polyarticular disease because of its relative safety, low-cost, and long follow-up data. It has been recently shown that patients who do not respond to 10 mg/sq. meter/week might respond to higher dosages. However, the plateau of efficacy of MTX was reached with parenteral administration of 15 mg/sq. meter/week, and a further increase in dosage was not associated with any additional therapeutic benefit⁶.

The availability of biologic agents, in particular the anti-TNF α drugs, has greatly improved the prognosis in cases who are resistant to methotrexate treatment. The efficacy of these drugs in JIA has been shown both in open (for infliximab)⁷ and controlled (for etanercept)⁸ studies.

Recently, Silverman and colleagues have compared the safety and efficacy of leflunomide with that of methotre-

Correspondence: R. Cimaz, M.D.
Pediatrics,
Via Commenda 9, 20122 Milano, Italy.
E-mail: Rolando.Cimaz@unimi.it

xate in the treatment of polyarticular JIA in a randomized, controlled trial⁹. The authors concluded that in patients with polyarticular JIA, both methotrexate and leflunomide resulted in high rates of clinical improvement, with a slightly greater rate for methotrexate.

Once clinical remission is achieved, it is always a problem to choose the right timing of drug discontinuation. Foell et al¹⁰ investigated whether the duration of MTX treatment after the induction of remission influences the subsequent duration of remission in patients with JIA, and the usefulness of a biologic marker (S100A8/S100A9) as a predictor for the stability of remission. The results suggested that the presence of residual subclinical synovial inflammation (as measured by S100A8/S100A9), not duration of MTX treatment after the induction of remission, influences the rate of relapse after discontinuation of MTX. However, the number of patients was small, and a larger controlled study specifically designed for this purpose is currently underway.

Systemic-onset JIA is one of the challenges of our clinics. There are some cases who are totally steroid-dependent, and in whom nothing seems to work. Recently, Pascual et al. have demonstrated the role of interleukin-1 in the disease pathogenesis, as well as the efficacy of a recombinant IL-1 receptor antagonist in an open study on nine patients who were refractory to other therapies¹¹. Complete remission was obtained in seven patients, and partial response in the other two.

Since interleukin-6 is also known to be one of the key mediators in this disorder, treatment with recombinant human anti-interleukin-6 receptor monoclonal antibody (MRA) has been tried in children with systemic-onset JIA refractory to high-dose, long-term corticosteroids¹². An individual escalating-dose trial was conducted in 11 children with active disease. MRA abruptly reduced disease activity in 10 of these patients, as assessed by the occurrence of febrile episodes, active arthritis, Childhood Health Assessment Questionnaire, and acute-phase reactants. The drug was well tolerated. However, larger controlled studies are needed before drawing any firm conclusions.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is not uncommon in children, since in about 15% of all cases the disease begins in childhood. It is associated with frequent organ system damage and influences the normal physical and psycho-social development of patients¹³.

With regard to etiopathogenesis, an important role for interferon- α (IFN- α) has been recognized, without substantial differences between children and adults with regard to leukocyte gene expression profiles. Blanco et al. hypothesized that the disease may be caused by alterations in the functions of dendritic cells. Indeed, monocytes from SLE patients' blood were found to function as

antigen-presenting cells *in vitro*, and sera from SLE patients induced normal monocytes to differentiate into dendritic cells. The capacity of SLE sera to induce DC differentiation correlated with disease activity and depended on the actions of IFN- α ¹⁴.

The survival of newly diagnosed SLE children has increased, the major reason for death being now infections, as opposed to renal failure as in the past. While a survival of 80-85% during a follow-up of 5-10 years was considered satisfactory in the past; the goal of new therapies is to obtain both a more prolonged survival and a reduced organ system damage. Renal and cerebral involvement are the major concerns in SLE children, and require an early aggressive therapeutic approach in order to reduce the degree of disease morbidity and mortality. Males and females seem not to have a different outcome in this regard¹⁵.

Azathioprine has been used for at least 30 years as second-line agent, but controlled trials are lacking in childhood. Anecdotal reports suggest that cyclosporin may allow the tapering steroids and better control of disease activity; however, hypertension and increased serum creatinine limit its use in children with renal involvement. Cytoxan pulses are now the first line treatment for severe lupus nephritis¹⁶; promising results have been reported in adults with Mycophenolate Mofetil (MMF), a novel immunosuppressive agent. The experience in childhood is limited to small case series¹⁷. Even though long-term follow-up is not available, MMF seems a promising drug for the treatment of severe juvenile SLE. Wulfraet et al. report autologous stem cell transplantation with sustained control of disease activity, off any medication, in two adolescents with intractable disease¹⁸. A long-term follow-up is however necessary, as well as strict inclusion criteria that should also consider the high risk of the procedure itself. Of the new biological therapies, in pediatrics anti-CD20 (Rituximab) seem to be the more promising agent¹⁹. No controlled trials are yet available.

Among short and long-term complications, osteopenia and osteoporosis are certainly a major risk, due to decreased sun exposure, inflammatory disease activity, and corticosteroid use²⁰. The use of bisphosphonates in patients with low bone density has significantly increased bone mass²¹. Accelerated atherosclerosis with carotid media-intima thickness²² and abnormalities in lipoprotein oxidation²³ are another major concern. Soep et al²⁴ investigated atherosclerotic risk factors and endothelial function in pediatric SLE. Lipoproteins, oxidized state, autoantibodies to oxidized low-density lipoprotein, and endothelial function (brachial artery reactivity) were measured. Patients had significantly decreased mean levels of high-density lipoprotein cholesterol and apolipoprotein A-I when compared to controls. Due to the risk of atherosclerotic coronary artery disease, the profile of plasma lipids should therefore be evaluated in all SLE children in order

to prevent early myocardial infarction. The best preventive strategies include no smoking, low-fat diet and physical activity. The role of antimalarials as lipid-lowering effect is known in adults, but studies of their usefulness in children are lacking.

JUVENILE DERMATOMYOSITIS

Idiopathic inflammatory myopathies are rare in childhood and display a less heterogeneous pattern than in adults. Juvenile dermatomyositis (JDM) with the characteristic skin and muscle abnormalities represents the most common form in childhood²⁵. Recently, Mendez et al evaluated the incidence of JDM in the United States; the estimated annual incidence rates ranged from 2.5 to 4.1 cases per million children²⁶. The results of the study provide evidence for sex, and possibly racial differences in the risk of JDM in the U.S., with girls affected more than boys (ratio 2.3:1), and white non-Hispanic and African-American children more frequently affected than Hispanic.

The etiology of JDM is still unknown: despite serological evidence of coxsackievirus B infection, the search of viral genomes in cells from JDM patients by polymerase chain reaction has not been fruitful. On the contrary, juvenile dermatomyositis has seen advances both in diagnostic procedures and in therapeutic approaches.

A recent study demonstrated the usefulness of MRI as a quantitative measure of muscle inflammation, and showed a good correlation with measures of disease activity. The MRI T2 relaxation times in the thigh muscle were significantly increased in patients with active JDM compared with those with inactive JDM and healthy children, indicating a detectable increase in inflammation within the muscles²⁷. There were also good correlations between the MRI scores and measures of muscle strength and function, but no correlation between the MRI and muscle enzymes.

Light microscopic and immunohistochemical analysis of muscle biopsy specimens from 10 patients with early JDM was performed to assess expression of MHC Class I genes²⁸. Class I gene overexpression was evident on muscle fibers in all samples, even in a biopsy reported as normal by conventional histology. MHC Class I gene overexpression is an early event in JDM and may occur in the absence of lymphocytic infiltration and muscle damage.

The outcome of the disease has dramatically improved since the introduction of corticosteroids, with a marked decrease in mortality. Conventionally, either oral prednisone (2 g/kg/day in 2-4 divided doses) and/or methylprednisolone pulses (30 mg/kg, max 1 g/day) are administered until a fall in the serum levels of muscle enzymes, and then gradually tapered. Since not all children respond to steroid treatment; intravenous gamma-globulins (IVIG), methotrexate, and cyclosporin A, alone or in combination, have all been used for refractory cases. In a retrospective review study of 12 patients with severe

refractory JDM, after 6 months of treatment with intravenous cyclophosphamide (0.5-1 g/m²) administered monthly, 10 patients showed a significant improvement in muscle function as assessed by the Childhood Myositis Assessment Scale, muscle strength, global extramuscular disease score, skin disease severity, and LDH levels²⁹. Clinical improvement was maintained after discontinuation of cyclophosphamide (follow-up duration 0.5-7 years), and no severe side effects were seen.

Calcinosis is one of the most severe complications of JDM, and disabling calcifications still occur in about one third of patients. Long-standing active disease, a delay in the initial appropriate treatment, and a short duration of steroid treatment are thought to be associated with the development of calcinosis, while aggressive management may result in decreased incidence³⁰. The pathogenesis of calcinosis is poorly understood, but an association with inflammation is supported by the presence of cytokines (IL-6, IL-1, and TNF-alpha) in the milky fluid obtained from calcium deposits³¹. The approaches to treating this complication are still anecdotal; moreover, it has to be known that in about half of the cases it can reduce spontaneously, and therefore any new possible success might just be due to natural history of the disease. Only placebo-controlled trials would answer this question, but to show a statistically significant superiority of any drug regimen, very large numbers would be needed.

The impact of corticosteroids on bone mineral density has been studied in 15 children with JDM, and low BMD values were found by DXA in the majority of cases, with persistent or worsening osteopenia in patients with ongoing active disease³². Bisphosphonates, a group of anti-resorptive agents that have been shown to be effective in osteogenesis imperfecta, have proven to be efficacious in this group of patients as well²¹.

KAWASAKI DISEASE

Kawasaki disease (KD), the most common systemic vasculitis in childhood after Henoch-Shönlein Purpura, is the major cause of acquired heart disease in children in the United Kingdom and USA, and may be a risk factor for adult ischemic heart disease. Despite numerous efforts, there is still no diagnostic test available for KD, and the diagnosis is based on clinical criteria after the exclusion of other diseases presenting with high and persistent fever. While from the clinical point of view there have been no recent advances, novel findings in pathogenesis warrant some considerations.

Despite numerous studies the cause of KD remains uncertain. The role of an infectious trigger inducing the disease in a genetically susceptible host is strongly suggested by the epidemiology of the disease in Japanese and North American epidemics, resembling the spread of viral or bacterial infections. The peak incidence in early childhood and the virtual absence of KD in adulthood sug-

gests that a possible causative agent could be a microbe, with acquired immunity by adulthood. The rarity of illness in infants in the first months of life suggests passive protection by maternal antibodies. KD has some similarities to toxin-mediated diseases, both from a clinical and from an immunological point of view. The role of one or more superantigens capable of stimulating large numbers of T-cells produced by certain strains of *Staphylococcus* or *Streptococcus* has been discussed in the etiology of KD, but no general consensus has been achieved. After the first reports by Abe et al^{33,34} describing selective expansion of V β 2 + and V β 8.1 + T cells in patients with acute KD, several other similar studies have been published, both with positive and with negative evidence for a superantigen-driven process³⁵⁻³⁷. Pro-inflammatory cytokines have been thought to play a role in the disease pathogenesis, and preliminary evidence for a genetic predisposition to elevated TNF- α levels in KD patients has been demonstrated³⁸. An interesting hypothesis refers to the role of IgA plasma cells that have been found in the vascular walls of KD patients; an oligoclonal pattern has been demonstrated, consistent with an antigen-driven immune response^{39,40}. The nature of this antigen is however still unknown.

With regard to prognosis, it is now recognized that subjects who suffered from KD in childhood might have long-term consequences, such as vascular function abnormalities and premature atherosclerosis⁴¹⁻⁴⁴. The only novel findings regarding treatment are represented by the anecdotal reports or small series describing clinical response with corticosteroids, and more recently with anti-TNF agents⁴⁵ in patients who were refractory to IVIG. Results of controlled trials currently in progress are not available at the present time.

REFERENCES

- Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: Second Revision, Edmonton, 2001. *J Rheumatol*. 2004;31:390-2.
- Knight AC, Dardzinski BJ, Laor T, Graham TB. Magnetic resonance imaging evaluation of the effects of juvenile rheumatoid arthritis on distal femoral weight-bearing cartilage. *Arthritis Rheum*. 2004;50:901-5.
- Falcini F, Bindi G, Ermini M, Galluzzi F, Poggi G, Rossi S, et al. Comparison of quantitative calcaneal ultrasound and dual energy X-ray absorptiometry in the evaluation of osteoporotic risk in children with chronic rheumatic diseases. *Calcified Tissue Int*. 2000;67:19-23.
- Falcini F, Bindi G, Simonini G, Stagi S, Galluzzi F, Masi L, et al. Bone status evaluation with calcaneal ultrasound in children with chronic rheumatic diseases. A one year follow-up study. *J Rheumatol*. 2003;30:179-84.
- Roth J, Palm C, Scheunemann I, Ranke MB, Schweitzer R, Dannecker GE. Musculoskeletal abnormalities of the forearm in patients with juvenile idiopathic arthritis relate mainly to bone geometry. *Arthritis Rheum*. 2004;50:1277-85.
- Ruperto N, Murray KJ, Gerloni V, Wulffraat N, De Oliveira SK, Falcini F, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum*. 2004;50:2191-201.
- Gerloni V, Pontikaki I, Gattinara M, Desiati F, Lupi E, Lurati A, et al. Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor alpha monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: Results of an open-label prospective study. *Arthritis Rheum*. 2005;52:548-53.
- Lovell DJ, Giannini ED, Reiff A, Cawkwell G, Silverman ED, Nocton JJ, et al. for the Pediatric Rheumatology Collaborative Study Group. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med*. 2000;342:763-9.
- Silverman E, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P, et al. Leflunomide in Juvenile Rheumatoid Arthritis (JRA) Investigator Group. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med*. 2005;352:1655-66.
- Foell D, Frosch M, Schulze zur Wiesch A, Vogl T, Sorg C, Roth J. Methotrexate treatment in juvenile idiopathic arthritis: When is the right time to stop? *Ann Rheum Dis*. 2004;63:206-8.
- Pascual V, Allantaz F, Arce E, Punaro M, Bancherau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med*. 2005;201:1479-86.
- Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, Mori M, et al. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum*. 2005;52:818-25.
- Ravelli A, Duarte-Salazar C, Buratti S, Reiff A, Bernstein B, Maldonado-Velázquez MR, et al. Assessment of damage in juvenile-onset systemic lupus erythematosus: A multicentre cohort study. *Arthritis Care Research*. 2003;49:501-7.
- Blanco P, Palucka AK, Gill M, Pascual V, Banchereau J. Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. *Science*. 2001;294:1540-3.
- Miettunen PM, Ortiz-Álvarez O, Petty RE, Cimaz R, Malleson PN, Cabral DA, et al. Gender and ethnic origin have no effect on long-term outcome of childhood-onset systemic lupus erythematosus. *J Rheumatol*. 2004;31:1650-4.
- Lehman TJA, Onel KB. Intermittent intravenous cyclophosphamide arrests progression of the renal toxicity index in childhood systemic lupus erythematosus. *J Pediatr*. 2000;136:243-7.
- Buratti S, Szer IS, Spencer CH, Bartosh S, Reiff A. Mycophenolate mofetil treatment of severe renal disease in pediatric onset systemic lupus erythematosus. *J Rheumatol*. 2001;28:2103-8.
- Wulffraat NM, Sanders EA, Kamphuis SS, Rijkers GT, Kuis W, Lilien M, et al. Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus. *Arthritis Rheum*. 2001;44:728-31.
- Edelbauer M, Jungraithmayr T, Zimmerhackl LB. Rituximab in childhood systemic lupus erythematosus refractory to conventional immunosuppression: Case report. *Pediatr Nephrol*. 2005;20:811-3.
- Lilleby V, Lien G, Frey Frosie K, Haugen M, Flato B, Forre O. Frequency of osteopenia in children and young adults with childhood-onset systemic lupus erythematosus. *Arthritis Rheum*. 2005;52:2051-9.
- Bianchi ML, Cimaz R, Bardare M, Zulian F, Lepore L, Buoncompagni A, et al. Efficacy and safety of alendronate for the

- treatment of osteoporosis in diffuse connective tissue diseases in children. *Arthritis Rheum.* 2000;43:1960-6.
22. Falaschi F, Ravelli A, Martignoni A, Migliavacca D, Sartori M, Pistorio A, et al. Nephrotic range proteinuria, the major risk factor for early atherosclerosis in juvenile-onset systemic lupus erythematosus. *Arthritis Rheum.* 2000;43:1405-9.
 23. Posadas-Romero C, Torres-Tamayo M, Zamora-González J, Aguilar-Herrera BE, Posadas-Sánchez R, Cardoso-Saldana G, et al. High insulin levels and increased low-density lipoprotein oxidizability in pediatric patients with systemic lupus erythematosus. *Arthritis Rheum.* 2004;50:160-5.
 24. Soep JB, Mietus-Snyder M, Malloy MJ, Witztum JL, Von Scheven E. Assessment of atherosclerotic risk factors and endothelial function in children and young adults with pediatric-onset systemic lupus erythematosus. *Arthritis Rheum.* 2004;51:451-7.
 25. Ramanan AV, Feldman BM. Clinical features and outcomes of juvenile dermatomyositis and other childhood onset myositis syndromes. *Rheum Dis Clin North Am.* 2002;28:833-7.
 26. Mendez EP, Lipton R, Ramsey-Goldman R, Roettcher P, Bowyer S, Dyer A, et al. US incidence of juvenile dermatomyositis, 1995-1998; results from the National Institute of Arthritis and Musculoskeletal and Skin disease Registry. *Arthritis Rheum.* 2003;49:300-5.
 27. Maillard S, Jones R, Owens C, Pilkington C, Woo P, Wedderburn LR, et al. Quantitative assessment of MRI T2 relaxation time of thigh muscles in juvenile dermatomyositis. *Rheumatology.* 2004;43:603-8.
 28. Li CK, Varsani H, Holton JL, Gao B, Woo P, Wedderburn L. MHC class I overexpression on muscles in early juvenile dermatomyositis. *J Rheumatol.* 2004;31:605-9.
 29. Riley P, Maillard S, Wedderburn LR, Woo P, Murray KJ, Pilkington C. Intravenous cyclophosphamide pulse therapy in juvenile dermatomyositis: A review of efficacy and safety. *Rheumatology.* 2004;43:491-6.
 30. Fisler RE, Liang MG, Fuhlbrigge RC, Yalcindag A, Sundel RP. Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. *J Am Acad Dermatol.* 2002;47:505-11.
 31. Mukamel M, Horev G, Mimouni M. New insight into calcinosis of juvenile dermatomyositis. A study of composition and treatment. *J Pediatr.* 2001;138:763-6.
 32. Stewart WA, Acott PD, Salisbury SR, Lang BA. Bone mineral density in juvenile dermatomyositis: Assessment using dual X-ray absorptiometry. *Arthritis Rheum.* 2003;48:2294-8.
 33. Abe J, Kotzin BL, Judo K, Melish ME, Glode MP, Koshaka T, et al. Selective expansion of T cells expressing T-cell receptor variable regions V beta 2 and V beta 8 in Kawasaki disease. *Proc Natl Acad Sci U S A.* 1992;89:4066-70.
 34. Abe J, Kotzin BL, Meissner C, Melish ME, Takahashi M, Fulton D, et al. Characterization of T-cell repertoire changes in acute Kawasaki disease. *J Exp Med.* 1993;177:791-6.
 35. Choi IH, Chwae YJ, Shim WS, Kim DS, Kwon DH, Kim JD, et al. Clonal expansion of CD8+ T cells in Kawasaki disease. *J Immunol.* 1997;159:481-6.
 36. Pietra BA, De Inocencio J, Giannini EH, Hirsch R. T cell receptor V beta family repertoire and T cell activation markers in Kawasaki disease. *J Immunol.* 1994;153:1881-8.
 37. Leung DYM, Meissner HC, Shulman ST, Mason WH, Gerber MA, Glode MP, et al. Prevalence of superantigen-secreting bacteria in patients with Kawasaki disease. *J Pediatr.* 2002;140:742-6.
 38. Quasney MW, Bronstein DE, Cantor RM, Zhang Q, Stroupe C, Shike H, et al. Increased frequency of alleles associated with elevated Tumor Necrosis Factor alpha levels in children with Kawasaki disease. *Pediatr Res.* 2001;49:686-90.
 39. Rowley AH, Shulman ST, Spike BT, Mask CA, Baker SC. Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. *J Immunol.* 2001;166:1334-43.
 40. Rowley TF, Al-Shamkhani A. Stimulation by soluble CD70 promotes strong primary and secondary CD8+ cytotoxic T cell responses in vivo. *J Immunol.* 2004;172:6039-46.
 41. Nakamura Y, Yanagawa H, Harada K, Kato H, Kawasaki T. Mortality among persons with a history of Kawasaki disease in Japan: Existence of cardiac sequelae elevated the mortality. *J Epidemiol.* 2000;10:372-5.
 42. Silva AA, Maeno Y, Hashmi A, Smallhorn JF, Silverman ED, McCrindle BW. Cardiovascular risk factors after Kawasaki disease: A case-control study. *J Pediatr.* 2001;138:400-5.
 43. Iemura M, Ishii M, Sugimura T, Akagi T, Kato H. Long term consequences of regressed coronary aneurysms after Kawasaki disease: Vascular wall morphology and function. *Heart.* 2000;83:307-1.
 44. Tsuda E, Kamiya T, Kimura K, Ono Y, Echigo S. Coronary artery dilatation exceeding 4.0 mm during acute Kawasaki disease predicts a high probability of subsequent late intima-medial thickening. *Pediatr Cardiol.* 2002;23:9-14.
 45. Burns JC, Mason WH, Hauger SB, Janai H, Bastian JF, Wohlley JD, et al. Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr.* 2005;146:662-7.