# Treatment Options for Refractory Kawasaki Disease: Alternative Treatments for Infliximab Nonresponders

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**Abstract** In a recent study, infliximab (IFX) therapy resulted in dramatic improvement in 85–90 % of children with Kawasaki disease who did not respond to repeated intravenous immunoglobulin (IVIG) infusion or steroid therapy as second-line treatment. Although studies have confirmed the clinical efficacy and safety of IFX therapy in children with refractory Kawasaki disease, there is no consensus regarding treatment of IFX nonresponse, which is defined as the presence of persistent fever (>37 °C) despite optimal treatment. In a treatment algorithm from two Japanese institutions, IFX was given to children who did not respond to second IVIG or methylprednisolone pulse (IMP) therapy. Overall, 10–26 % were IFX nonresponders, and treatments for this group included IVIG, methylprednisolone pulse, and cyclosporin A. Persistent fever resolved in IFX nonresponders after these additional treatments, although some patients developed coronary artery abnormalities. There has been no evidence-based study of optimal treatment for IFX nonresponders. If fever or elevation of C-reactive protein does not resolve after IFX therapy, therapies other than IFX, such as re-IVIG, re-IMP, and other immunosuppressive agents, should be started.

**Keywords** Infliximab • Intravenous immunoglobulin • Refractory Kawasaki disease • Methylprednisolone pulse

## Introduction

Approximately 20 % of children with Kawasaki disease (KD) have persistent or recurrent fever at or later than 36 h after initial intravenous immunoglobulin (IVIG) administration [1]. Nonresponders to initial IVIG have a higher risk of developing coronary artery abnormalities (CAAs). A second dose of IVIG and steroid pulse therapy are used as second-line treatment strategies. However, a small subset of patients will remain febrile after such therapies. There are no guidelines for

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management of these children, who have persistent inflammation and are at high risk for CAAs. Reported third-line therapies for refractory KD include infliximab (IFX).

IFX is a humanized mouse monoclonal antibody that binds to tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine that has an important role in rheumatoid arthritis and other vasculitis syndromes. TNF-α levels are elevated in patients with acute KD [2], and the highest serum levels were observed in patients with CAAs [3]. Clinical studies have investigated the effectiveness of IFX therapy for IVIG-resistant KD. Although several found that IFX had potential benefits for this population [4–6], a recent study reported that the incidence of IFX nonresponse was 11.2 % [4]. Unfortunately, there have been no large studies of treatment strategies for this population. This chapter describes recent findings from patients with rheumatic disease and KD that did not respond to treatment with IFX.

## IFX Nonresponders

### *IFX Therapy in KD*

In a recent study of IFX therapy for children with KD who did not respond to repeated IVIG infusion or steroid therapy, IFX resulted in dramatic improvements in 85–90 % of children, without treatment-related serious adverse events. In Japan, IFX therapy has been used since 2006 for cases of refractory KD. As was noted in previous US reports, Japanese patients with KD markedly improved, with no IFX-related adverse events [7–10]. These findings suggest that IFX therapy reduces the risk of subsequent CAAs in patients who have an unsatisfactory therapeutic response to conventional treatments. Numerous studies have confirmed the clinical efficacy and safety profile of IFX therapy in children with refractory KD. However, no treatment strategies for IFX nonresponders are available.

### *IFX Nonresponse in Inflammatory Disease*

In pediatric populations, IFX has been approved for treatment of immune-modulated inflammatory disorders such as Crohn's disease. Although data on IFX therapy in KD are limited, previous studies have investigated pediatric IFX non-responders with inflammatory bowel disease. In studies of children with Crohn's disease, clinical improvement was observed in children treated with 5 mg/kg IFX. Additionally, disease activity frequently relapsed after discontinuation of IFX treatment. A previous study found that 29 % of children with Crohn's disease were unresponsive to IFX, whereas 29 % had a prolonged response after discontinuation of IFX and 42 % were dependent on IFX therapy [11]. Similarly, several

studies investigated clinical response to IFX therapy in children with ulcerative colitis. Clinical improvement was not seen in approximately 25–35 % of these patients [12, 13].

## *Definition and Incidence of IFX Nonresponse in KD*

IFX nonresponse is defined as persistence of fever (>37 °C) despite optimal treatment for refractory KD, ie, IVIG or steroid. In a nonrandomized, open-label, single-center trial of 76 Japanese children unresponsive to additional IVIG therapy [5], 70 responded to IFX therapy. The remaining six children (8 %), who were nonresponsive to IFX, were treated with plasma exchange. However, 12 of the 76 patients (16 %) developed coronary artery dilatation and three had CAAs, whereas five had coronary dilatation and one had a CAA before IFX administration. All CAAs resolved during follow-up.

A phase III, randomized, double-blind, placebo-controlled trial of the clinical effect of IFX plus IVIG treatment on adverse outcomes in patients with refractory KD [4] showed no significant difference in the rate of treatment resistance (11.2 % for IFX vs 11.3 % for placebo) or CAA incidence between the two groups at 5 weeks, although the IFX group had faster resolution of fever and fewer days of hospitalization as compared with the placebo group. None of the patients who received IFX therapy developed serious adverse events. Children resistant to IFX received a second infusion of IVIG, but responsiveness was not described. The authors concluded that addition of IFX to IVIG as a first-line therapy did not reduce treatment resistance.

## *Treatment of IFX Nonresponders*

In a treatment algorithm from two Japanese institutions, IFX was given to nonresponders to second IVIG or methylprednisolone pulse (IMP) therapy (Fig. 1). Overall, 26 % of children were IFX nonresponders, and treatments for this group included IVIG (1 or 2 g/kg), IMP (15–30 mg/kg), and cyclosporin A (5 mg/kg/day, po). After these additional treatments, clinical improvements were noted in all nonresponders. There has been no evidence-based study of optimal treatment for children with KD who do not respond to IFX. Table 1 shows our proposed treatment for this population. Treatment options are based on those commonly used for other inflammatory diseases such as rheumatoid arthritis and Crohn's disease. In a study of the rate and reasons for discontinuation of IFX therapy in adults with active rheumatoid arthritis during a 10-year follow-up period [14], 34 of 144 patients (24 %) discontinued IFX therapy because of loss of effectiveness. Methotrexate and tacrolimus resulted in satisfactory clinical improvement in the treatment of rheumatoid arthritis in IFX nonresponders [15].

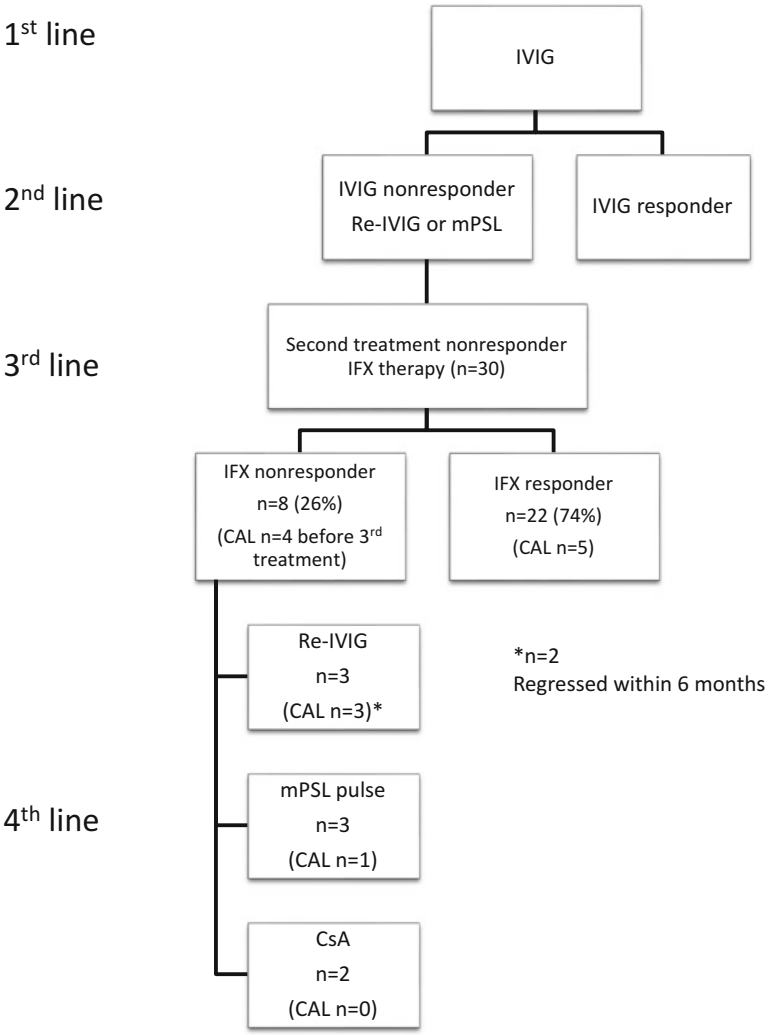


**Fig. 1** Treatment algorithm at two institutions. None of patients have development of new coronary artery abnormalities after IFX therapies. The 32nd annual meeting of the Japanese Society of Kawasaki Disease (unpublished data). *CsA* cyclosporin A, *IFX* infliximab, *IVIG* intravenous immunoglobulin, *mPSL* methylprednisolone

**Table 1** Proposed treatment plan for infliximab nonresponders

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| 1. Re-IVIG treatment |
| 2. Steroid: prednisolone or methylprednisolone pulse |
| 3. Immunosuppressive agents |
| (a) Other anti–TNF-α agent: etanercept, adalimumab |
| (b) Cyclosporin A |
| 4. Plasma exchange |

Transition to other TNF-α agents, such as etanercept and adalimumab, may also be effective for IFX nonresponders. Like IFX, etanercept is a TNF-α inhibitor and has been used as additional therapy for patients with refractory KD. Etanercept is approved by the US Food and Drug Administration for children older than 2 years with juvenile idiopathic arthritis. In an experimental study, etanercept significantly reduced arteritis severity as compared with IVIG, methylprednisolone, and cyclosporin A [16]. A mouse model of KD was induced by injecting *Candida albicans* water-soluble fractions. In a study of four agents, the severity of experimental vasculitis at 2 weeks was reduced by etanercept. Although IVIG and cyclosporin A attenuated inflammation, only etanercept significantly improved vasculitis. A prospective, open-label trial evaluated the clinical efficacy and safety profile in children with KD treated with etanercept [17]. The children, aged 6 months to 5 years, were all IVIG-resistant. Three doses of etanercept (0.8 mg/kg/dose) were given subcutaneously within 2 weeks after IVIG and resulted in resolution of prolonged fever, without serious adverse events. No CAAs developed after etanercept infusion. These findings suggest that etanercept is a satisfactory alternative immunosuppressive treatment for IVIG-resistant KD, although there are no data on etanercept treatment for KD patients who did not respond to IFX.

Adalimumab is another anti–TNF-α agent and has been approved for adults with rheumatoid disease. It improved inflammatory markers in patients who did not respond to IFX or etanercept, without serious adverse events [18].

Although transition to other immunosuppressive treatment is effective for IFX nonresponders, uptitration of IFX is another method for treating unresolved clinical symptoms. In a randomized, double-blind study of the efficacy and safety of 10 mg/kg and 3 mg/kg infliximab treatment for methotrexate-refractory rheumatoid arthritis [19], the higher dosage was beneficial for patients who had not responded to three infusions of 3 mg/kg. Incidence of adverse events did not differ between groups.

## Conclusion

IFX nonresponse is defined as persistent fever despite optimal treatment. Approximately 10–26 % of children with KD are IFX nonresponders. However, there has been no evidence-based study of optimal treatments for this population. Treatments for IFX nonresponders include IVIG, methylprednisolone pulse, and cyclosporin A.

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