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Utility of TNF-α as a Biomarker and the Possibility of anti-TNF-α Therapy for Kawasaki Diseases

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Abstract

Kawasaki disease (KD) is the most common systemic vasculitis syndrome, primarily affecting the coronary arteries. Timely treatment with high-dose intravenous immunoglobulin (IVIG) reduces the duration of fever and incidence of Coronary Artery Lesions (CAL). However, even after IVIG treatment ~5%-7% of patients develop aneurysms.

TNF-α is a cytokine with multiple biological effects produced primarily by monocytes and macrophages. In the last decade, TNF-α has been the focus of research aimed at uncovering its role during the acute phase of KD. Previous studies reported that TNF-α is responsible for the increase in its soluble receptors and is involved in the pathogenesis of the clinical features and CAL in KD.

Anti-TNF-α therapies, such as infliximab or etanercept, seem to be effective in controlling inflammation in patients with KD who fail to respond to IVIG. Several trials of the usage of infliximab as the first, second, or third line therapy for KD since 2004 showed that infliximab was safe and well tolerated, and patients treated with infliximab had fewer days of fever. Etanercept was recently shown to be safe and well tolerated as adjunctive initial therapy with IVIG in a small study of children with KD.

Keywords: Kawasaki disease; TNF-α

Abbreviations: KD: Kawasaki Disease; CAL: Coronary Artery Lesion; TNF: Tumor Necrosis Factor; IVIG: Intravenous Immunoglobulin; TNFR: Tumor Necrosis Factor Alpha Receptor; sTNFR: Soluble Tumor Necrosis Factor Alpha Receptor

Introduction

Inflammation has often been considered to be a nonspecific response and to play a bridging role in the activation of adaptive immunity. However, it is now accepted that inflammation is the product of an independent innate immune system closely linked to the adaptive immune system. The key mediators of inflammation are inflammatory cytokines, as determined by multiple lines of evidence both in vitro and in vivo. Because of the crucial role of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, in the pathogenesis of autoimmune disorders, anticytokine treatment has been developed as a therapy for rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel diseases and Kawasaki disease (KD).

KD is the most common systemic vasculitis syndrome, primarily affecting small to medium-sized arteries, more particularly the coronary arteries [1]. KD was first described in 1967 and is now identified as the leading cause of acquired heart disease among children in developed countries [2]. The annual incidence of KD in children of Japanese descent is about 218 per 100,000 children less than five years of age, as compared with about 20 per 100,000 in the United States (US) [3,4]. Timely treatment with high-dose intravenous immunoglobulin (IVIG) reduces the duration of fever and incidence of coronary artery lesions (CAL). However, even after IVIG treatment, ~5%-7% of patients develop aneurysms [5]. To date, the pathogenesis of KD is still not been fully elucidated. Activation of innate and adaptive immune systems is thought to be a central feature of KD. There have been many reports on elevation of plasma levels of multiple inflammatory cytokines, such as TNF-α, interleukin -1b, IL-6, IL-8, and interferon-γ, during the acute phase of KD.

In the last decade, TNF-α has been focused on its role during the acute phase of KD. Here, we review the role of TNF-α, its usefulness as a biomarker, and the effectiveness of anti-TNF-α therapy in KD.

TNF-α

TNF-α is a cytokine with multiple biological effects produced primarily by monocytes and macrophages. TNF-α is a polypeptide cytokine mainly produced by stimulated monocytes, macrophages, and T-lymphocyte subsets. TNF-α plays a key role during the immune response, and it is a potent mediator of inflammatory mechanisms in normal immune surveillance and in pathologic conditions. TNF-α exerts its effects through two cell-surface receptors of 55 and 75 kDa (TNF-α soluble receptors [TNFR] 1 and TNFR 2, respectively) [6]. These cell surface receptors function as transducing elements, providing the intracellular signal for the response to TNF-α. TNFR1 is present on most cells, particularly on those that are susceptible to the cytotoxic action of TNF-α. TNFR2 is also present on many cell types, particularly those of myeloid origin, and it is strongly expressed on stimulated T and B cells.

The histological observation of the association between KD and TNF-α was reported in a 3-month-old female infant with incomplete KD who suddenly died despite IVIG, aspirin, steroid, and heparin treatment [7]. Postmortem examination confirmed the echocardiographically detected giant coronary aneurysms and showed occlusive thrombosis in the giant aneurysm of the left anterior descending coronary artery (LAD). The coronary arteries, including the giant LAD aneurysm, of the KD case showed macrophage infiltration, neoangiogenesis, and

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immunoreactivity for TNF-α, tissue factor (TF), and thrombopoietin (TPO).

The role of TNF-α in the immune response leading to vascular damage was showed in a murine model of KD using Lactobacillus casei cell wall extract (LCWE) to induce coronary arteritis, where rapid production of TNF-α in the peripheral immune system occurred after disease induction [8]. It was reported that rapid production of TNF-α in the peripheral immune system occurred after disease induction in a murine model of KD. This immune response became site-directed, with migration to the coronary arteries dependent on TNF-α-mediated events. The production of TNF-α in the heart was coincident with the presence of inflammatory infiltrate at the coronary arteries, which persisted during the development of aneurysms. Inflammation and elastin breakdown in the coronary vessels were completely eliminated in the absence of TNF-α effector functions.

Genetic studies also support a role for TNF-α in KD. A systematic review and meta-analysis identified a trend of association between the TNF-α-308 polymorphism and KD [9-13]. The TNF-α-308 polymorphism might be associated with KD via TNF-α production that could induce cell damage [14,15]. This association may be mediated by complex interactions affecting the inflammatory cascade, linkage disequilibrium, or gene interaction, given that the TNF-α-308 polymorphism is linked with nearby polymorphisms, either in the same region, such as TNF-α-238,-857,-863,-1031, or in the major histocompatibility complex (MHC) region, such as the human leukocyte antigen (HLA)-A1, -B8, and -DR3 alleles [13,16,17]

Previous studies reported that the serum or plasma levels of TNF-α before initial treatment in patients with KD were higher than those in patients in the convalescent stage and in healthy controls. TNF-α, soluble TNFR1 (sTNFR1), and soluble TNFR2 (sTNFR2) concentrations are increased in the acute phase of KD and are highest in children who subsequently develop coronary artery aneurysms [18,19]. TNF-α is responsible for the increase in its soluble receptors and is involved in the pathogenesis of the clinical features and CAL in KD [9,18-24]. However, other previous studies reported that the serum or plasma levels of TNF-α had no correlation with clinical and laboratory parameters (Table 1) [25-27]. These discrepancies may come from the stability of TNF-α. Because TNF-α is cleared very rapidly from the circulation, its levels at a given moment may not necessarily reflect local production in the preceding hours [28]. TNF-α is frequently undetectable, and some assays are unable to detect TNF-α bound to sTNFRs; on the other hand, sTNFRs are very stable and can also be determined in stored sera. In addition, serum levels of both sTNFR1 and sTNFR2 correlate well with those of TNF-α [29-31]. Recent studies showed that several immunoassays for TNF-α gave markedly different results even when using international standards [32,33]. Another reason for these discrepancies might be related to the presence of TNF-α/sTNFR complexes and the levels of sTNFR1 or sTNFR2 [34,35]. In addition to sTNFRs in plasma, other factors, including the presence of monomeric or oligomeric forms, and of degradation products of TNF-α, or binding of TNF-α to other molecules, such as immunoglobulins or α2-macroglobulin, may be responsible for these discrepancies by altering TNF-α antigenic properties [36-39]. The difficulties related to TNF-α measurement in plasma make it difficult to compare the results obtained in different laboratories using different methods.

Anti-TNF-α Therapy

Infliximab

On the basis of the evidence that serum levels of the proinflammatory cytokine TNF-α are elevated in patients with acute KD, with the highest levels observed in patients who develop coronary artery abnormalities, TNF-α blockade using anti-TNF-α therapy, such as infliximab and etanercept, might be thought to be effective in controlling inflammation in patients with KD who fail to respond to IVIG (Figure 1 and Table 2) [19].

Infliximab (Remicade) is a chimeric murine/human immunoglobulin G (IgG)-1 monoclonal antibody that binds specifically to human TNF-α-1 [40] Infliximab is indicated for treating immune-modulated inflammatory disorders, including pediatric Crohn's disease [41]. The first case report of a child treated with infliximab for KD resistant to several doses of IVIG and methylprednisolone was published in 2004 [42]. This observation led to the trial and successful use of infliximab (5 mg/kg) as the third-line therapy in several case reports and small case series of KD patients with IVIG-resistant disease (Table 3) [42-46]. These reports were followed by a small US multicenter, randomized trial of second IVIG infusion vs. infliximab in 24 children with KD after failure of initial treatment with IVIG. An analysis of the Pediatric Health Information System database from 2001 to 2006 showed that 14 of the 27 participating hospitals had administered infliximab to 48 patients for treatment-resistant KD [47] of these 48 patients, 12 had received infliximab as part of a phase 1 multicenter, randomized, prospective trial of second IVIG vs. infliximab for IVIG-resistant KD [23]. This study showed that infliximab was safe and well tolerated. Subsequently, a two-center retrospective review of IVIG-resistant patients treated with either a second course of IVIG (n=86) or infliximab (n=20) indicated that patients treated with infliximab had fewer days of fever (median 8 vs. 10 days, p=0.028) and shorter lengths of hospitals stay (median 5.5 vs. 6.0 days, p=0.04) than those given a second IVIG dose [48]. Additional prospective case series from Korea and Japan have also demonstrated the efficacy of infliximab in 13 of 16 (81%) and 18 of 20 (90%) patients with IVIG-resistant KD, respectively [49,50]. Taken together, these studies suggest that a single infusion of 5mg/kg of infliximab is safe and well tolerated and attributed to refractory KD (Table 2).

To further evaluate the role of infliximab in the treatment of KD, a phase 3, randomized, double-blind, placebo-controlled trial was undertaken in two children's hospitals in the US to assess the addition of infliximab (5mg/ kg) to standard therapy [51]. In total, 196 patients were enrolled and randomized: 98 to the infliximab group and 98 to the placebo. Treatment resistance rate did not differ significantly between the infliximab group and the placebo group. Compared with the placebo group, participants given infliximab had fewer days of fever (median 1 day for infliximab vs. 2 days for placebo; p<0.0001). The infliximab group had a greater mean reduction in C-reactive protein concentration (p=0.0003) and in absolute neutrophil count (p=0.024) at 24h after treatment than did those given placebo, but, by week 2, this difference was not significant. No significant differences were recorded between the two groups in proximal coronary artery Z scores or any other laboratory markers of inflammation measured. They concluded that the addition of infliximab to primary treatment in acute KD did not reduce treatment resistance.

To clarify the role of infliximab in the patients with KD who were resistant to initial and additional therapies and were treated with infliximab, Hirono K et al. investigated the dynamic changes of

Year	Number of patients	Serum/ plasma	TNF-α/ sTNFR	Concentration level							Significance between patients and controls	Significance between CAL and nonCAL	References
				Pre-initial treatment	Post-initial treatment	2ndtreatment (nonresponder)	Convalescent	Control	Patient with CAL	Patient without CAL			
2014	40	serum	TNF-α	3.4 ± 18.5 pg/mL				0.32 ± 0.67 pg/mL (FC, n=32) 0.59 ± 1.03 pg/mL (AC, n=15)	9.21 ± 31.10 pg/mL (n=12)	0.21 ± 0.22 pg/mL (n=28)	no	no	[25]
2013	143	serum	TNF-α	2.5 pg/mL	2.4 pg/mL		2.5 pg/mL (n=33)	3.8 pg/mL (n=80)			no	N/A	[26]
2012	39	plasma	TNF-α	33.2 ± 63.1 pg/ mL	18.3 ± 61.8 pg/mL			13.8 ± 61.1 pg/mL (n=15)			yes	N/A	[18]
2003	24	serum	TNF-α	24.1 ± 9.4 pg/mL	11.8 ± 5.8 pg/mL			10.4 ± 4.9 pg/mL (n=12)			yes	N/A	[9]
2000	30	plasma	TNF-α	15.4 ± 11.5 pg/ mL			8.8 ± 7.1 pg/mL	7.8 ± 6.9 (children, n=17) 8.2 ± 7.4 (adults, n=10)			no	N/A	[27]
1990	45	serum	TNF-α	18 cases (37.8%) >10 units/ mL				<10 units/ mL	10/11 (90.1%) >10 units/ mL	7/34 (20.6%) >10 units/ mL	yes	yes	[19]
1989	39	serum	TNF-α						51.1 ± 13.6 pg/ mL (n=4)	30.4 ± 15.8 pg/mL (n=35)	yes	yes	[20]
1988	30	serum	TNF-α	12 cases (40%) >10 units/ mL				<10 units/ mL	6/6 (100%) >10 units/ mL	6/24 (25%) >10 units/ mL	yes	yes	[21]
2009		serum	sTNFR1	0.58 ± 0.18 ng/ mL (Res, n=18)	0.33 ng/ mL (Res, n=18)	0.71 ± 0.16 ng/ mL (IFX, n=11) 0.60 ± 0.24 ng/ mL (nonRes, n=14)	0.39 ± 0.16 ng/ mL (IFX, n=11) 0.47 ± 0.22ng/ mL (nonRes, n=14)	0.22 ± 0.08 ng/mL (n=33)			yes	N/A	[22]
2008	24	serum	sTNFR1, 2		sTNFR1 8164.0 pg/mL sTNFR2 4405.5 pg/mL (nonRes, n=11)	sTNFR1 12428.0 pg/mL sTNFR2 5784.0 pg/mL (IFX, n=12)					yes	N/A	[23]
1994	48	serum	sTNFR1	6.3 ± 4.2 ng/mL			1.6 ± 0.8 ng/mL	1.5 ± 0.5 ng/mL	13.9 ± 3.5 ng/mL	5.4 ± 3.2 ng/ mL	yes	yes	[24]

TNF-α: Tumor Necrosis Factor-α; sTNFR : Soluble Tumor Necrosis Factor-α Receptor; CAL: Coronary Artery Lesions; FC: Febrile Controls; AC: Afebrile Controls; IFX: Infliximab; nonRes, nonresponders; Res, responders

Table 1: Recent studies of TNF-α and TNFR as a biomarker in KD.

cytokines during infliximab treatment [22]. They measured serum levels of sTNFR1 and interleukin (IL)-6, as well as vascular endothelial growth factor (VEGF), and the damage-associated molecular pattern (DAMP) molecules myeloid-related protein (MRP) 8/MRP14 and S100A12 sequentially. Although serum levels of proinflammatory cytokines decreased dramatically after infliximab treatment, DAMP molecules, VEGF, and markers of local tissue damage were not suppressed. In IVIG responders, all cytokines decreased markedly after IVIG treatment. Different behaviors of proinflammatory cytokines compared with those of DAMP molecules and VEGF after infliximab treatment suggest that infliximab is effective for the suppression of cytokine-mediated inflammation, but could not completely block local vasculitis.

To investigate the mechanism of action of infliximab therapy in the setting of KD, Ogihara Y et al. used microarray platforms to determine the transcript abundance profiles in whole blood obtained from eight IVIG-resistant KD subjects treated with infliximab therapy and compared them with those in initially IVIG-responsive subjects [52]. The pathway analysis showed a reduced abundance of transcripts in the nucleotide-binding oligomerization domain, matrix metalloproteinase (MMP), and inflammatory cytokine pathways and an increased abundance of transcripts in the T-cell receptor, apoptosis, tumor growth factor (TGF)-β, and IL-2 pathways in the IVIG-resistant, infliximab-treated subjects. The transcript abundance, which was found to be related to signaling pathways of KD inflammation, such as those involving IL-1, IL-6, and TNF-α, changed significantly following

the administration of infliximab therapy, suggesting that infliximab therapy regulates important cytokine signaling activities involved in KD inflammation by blocking TNF-α, which may be critical for regulating IVIG resistance factors.

These two observations regarding the dynamic changes of cytokines in KD suggested that infliximab may regulate cytokine signaling relevant to KD inflammation via TNF-α blockade, but could not completely prevent local vasculitis because TNF-α may not have a central role in the development of vasculitis.

Etanercept

Etanercept (Enbrel) is another TNF-α inhibitor that has been studied in a small number of KD patients. Etanercept is a sTNFR and functions as a TNF antagonist with a proposed similar mechanism of action to infliximab in the treatment of KD (Figure 1 and Table 2). Similarly to infliximab, etanercept has been widely used in a broad array of autoimmune and inflammatory diseases. Etanercept was recently shown to be safe and well tolerated as adjunctive initial therapy with IVIG in a small study of children with KD [53]. None of the patients treated in this study-required retreatment. On the basis of these preliminary data, there is a proposed multicenter, double-blind, randomized, placebo-controlled trial looking at the efficacy of etanercept in addition to IVIG plus aspirin for initial therapy at reducing the rate of IVIG-resistant disease [54].

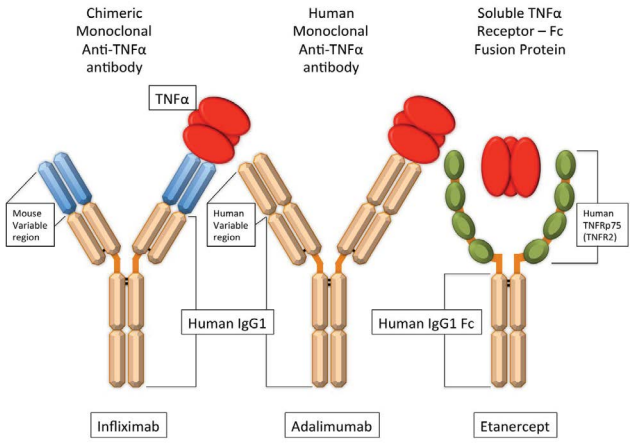

Figure 1: Construct of anti-TNF-α biological agents.

Recently, three studies reported the role of two TNF-α blockers, infliximab and etanercept, using murine models of KD. Hui-Yuen JS et al. examined the role of TNF-α in the immune response leading to vascular damage in the mouse model of KD that involves the injection of LCWE [55]. Mice treated with the TNF-α-blocking agent etanercept, as well as TNFR1 knockout mice, were resistant to both coronary arteritis development and coronary aneurysm formation. It was concluded that TNF-α was necessary for the development of CAL in an animal model of KD. Oharaseki et al. studied the role of TNFα in a murine model of KD arteritis induced with Candida Albicans Water-Soluble fraction (CAWS) and treated with antiTNFα drugs (etanercept and infliximab) [56]. Their histopathological analysis revealed that the administration of etanercept to the mice reduced not only the incidence of vasculitis but also the scope of lesions and degree of inflammation. Ohashi R et al. reported that etanercept suppresses arteritis in a murine model of KD [51,57]. They compared the efficacy of IVIG, etanercept, methylprednisolone and cyclosporine-A in suppressing CAWS-induced vasculitis in DBA/2 mice. Etanercept was the most effective not only in suppressing inflammation but also in decreasing plasma cytokine levels, and there was a strong correlation between the extent of the vasculitis and the plasma TNF-α levels.

Generic name	Trade name	Structure	Antibody source	Mechanism of TNF-α inhibition	Half-life	Administration pathway
Infliximab	Remicade	25% murine, 75% human. Variable region of a mouse monoclonal anti-TNF-α antibody coupled to the construct region of a human IgG1	Human-mouse	Chimeric human–mouse IgG1 monoclonal antibody that inhibits binding of TNF-α	8-10 days	Intravenous
Adalimumab	Humira	100% human peptide sequence and structure. Full-length human IgG1. Phage display technology resulting in human-derived variable regions and human IgG1; k constant regions	Human	Fully human IgG1 monoclonal antibody that inhibits binding of TNF-α	10-20 days	Subcutaneous
Etanercept	Enbrel	100% human peptide but artificial construction. Fusion protein made up of two soluble TNF receptor molecules (TNFR2) fused with the Fc fragment from human IgG1	Human + TNF-α receptor	Recombinant TNF-α receptor fusion protein that competitively inhibits the binding of TNF-α	3.0-5.5 days	Subcutaneous
TNF-α, tumor necrosis factor-α; IgG1, immunoglobulin G1						

Table 2: Biological characteristics of anti-TNF-α agents.

Anti-TNF-α drug	Year	Country	Illness day of IFX infusion	Timing of administration	Total	Additional therapy						CAL
						Total	IVIG	IVMP	IFX	PE	CsA	
Infliximab	2008	USA	7.5	2nd (n =12) 3rd (n =4)	16	3 (19%)	1	2	0	0	0	N/A (giant CAL 1)
Infliximab	2009	Japan	10.2 ± 1.8	3rd	11	3 (27%)	1	3	0	0	1	4 (36%)
Infliximab	2010	Korea	16.5 ± 6.3	3rd	16	3 (19%)	1	1	1	0	0	5 (31.2%)
Infliximab	2011	USA	7	2nd	20	3 (15%)	15	3	0	0	0	7 (35%)
Infliximab	2014	Japan	8.5 ± 0.14	3rd	76	6 (7.9%)	0	0	0	6	0	3 (3.8%)
Infliximab	2014	Japan	10.5	3rd	17	0 (0%)	0	0	0	0	0	4 (23.5%)
Infliximab	2014	USA	6	1st (with IVIG)	98	11 (11.2%)	2	0	0	0	0	26 (27.1%)
Etanercept	2010	USA	<10	2nd	15	0 (0%)	0	0	0	0	0	0 (0%)
TNF-α: Tumor Necrosis Factor-α; KD: Kawasaki Disease; IFX: Infliximab; IVIG: Intravenous Immunoglobulins; IVMP: Intravenous Methylprednisolone Pulse; PE: Plasma Exchange; CsA: Cyclosporin A; CAL: Coronary Artery Lesions.												

Table 3: Recent studies of anti-TNF-α therapy in KD.

These studies of KD murine models suggest that TNF-α has an important role in the pathogenesis of vasculitis in KD, and etanercept could potentially be a new effective therapy for arteritis in KD. Further clinical trials are required to confirm the efficacy and safety of etanercept therapy and establish its usefulness in the treatment of KD.

Limitations

We review the current knowledge regarding the role of TNF-α and the utilities of infliximab and etanercept. It has been suggest that TNF-α has an important role in the pathogenesis of vasculitis in KD and etanercept could be used as a new effective therapy for arteritis in KD. Further studies will be warranted to confirm the efficacy and safety of etanercept therapy and establish its usefulness in the treatment of KD.

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