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Overview of Pharmacological Treatment of Kawasaki Disease

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Contents

Abstract

Kawasaki disease has been researched for 32 years but its aetiology is still unknown. Conventional therapy for the disease includes corticosteroids and aspirin (acetylsalicylic acid) as anti-inflammatory and/or antithrombotic agents but they have not been proven to prevent coronary artery aneurysms. Although a high incidence of liver dysfunction in Japanese patients with Kawasaki disease receiving high dose aspirin (≥80 mg/kg/day) suggests racial differences in salicylate sensitivity, the duration of fever in patients receiving high dose aspirin is shorter than that in patients receiving moderate dosages (30 to 50 mg/kg/day). Furthermore, most corticosteroid-resistant patients were found to develop coronary artery aneurysms, many of which were large. With the clarification of the pathogenesis and clinical features of Kawasaki disease, advances in its treatment have been achieved. The introduction of high-dose intravenous γ-globulin (IVGG) was an epoch in this field and IVGG is now a standard therapy with the incidence of persistent coronary aneurysms 1.9% in children with the disease receiving IVGG. Today, research is mainly directed toward the treatment of IVGG-resistant patients. One to 3 days of pulsed doses of methylprednisolone (30 mg/kg/day) or readministration of IVGG 1 g/kg (once to several times) has been recommended for patients with IVGG-resistant Kawasaki disease.

Kawasaki disease, generalised vasculitis and organopathies of unknown aetiology, was first described by Dr Tomisaku Kawasaki in 1967 in Japan as the acute febrile mucocutaneous lymph node syndrome[1] with fever, rash, non-exudative conjunctivitis, inflammation of the oral mucosa, erythema and swelling of the hands and feet, and cervical adenitis. It was subsequently found to be the leading cause of acquired heart disease in children in both Japan and the US. It occurs more often in boys than in girls, with a ratio of about 1.5 : 1, and mostly in children younger than 5 years of age with a recurrence rate less than 2%. More than 140 000 cases were reported in Japan from 1967 through December 1996. Kawasaki disease has now been reported worldwide.

The occurrence of Kawasaki disease epidemics and the wave-like spread of such epidemics suggests that the disease is caused by a microbial agent. Onouchi et al.[2] reported that there is a close correlation between the speed of the epidemic spread of Kawasaki disease among cities in metropolitan areas and the number of daily passengers on intercity mass transportation. However, secondary cases occurring in contacts of affected patients are extremely rare.

Although an aetiological agent has not been identified, recent attention has focused on a family of enterotoxins produced by a variety of different strains of bacteria. These bind to specific variable beta regions of the T-cell receptor in conjunction with major histocompatibility complex class 2 antigens and act as superantigens to induce T-cell proliferation and cytokine release.[3] Immunological findings in Kawasaki disease are similar to those induced by the enterotoxin family.

There is no specific diagnostic test for Kawasaki disease, but clinical diagnostic guidelines proposed by the Kawasaki Disease Research Committee, supported by the Ministry of Health and Welfare of Japan, assist in the diagnosis of typical Kawasaki disease (table I).[4]

The clinical features of Kawasaki disease are those of acute self-limiting febrile illness. However, the major pathological features are carditis and a vasculitis affecting small and medium sized blood vessels throughout the body. The coronary circulation is particularly affected, with coronary artery aneurysm (the major life-threatening complication) developing in 15 to 25% of children with the disease. The main causes of death in the acute phase of Kawasaki disease are congestive heart failure due to carditis, and rupture or thrombotic occlusion of coronary artery aneurysm.[5-7] Therefore, treatment is intially aimed at reducing inflammation (particularly in the coronary arterial wall and myocardium) as well as preventing coronary thrombosis by inhibiting platelet aggregation.

Conventional therapy for Kawasaki disease includes corticosteroids[8] and aspirin[9] as anti-inflammatory and/or antithrombotic agents, but they have not been proved to prevent coronary artery aneurysms. High dose intravenous γ-globulin (IVGG), reported in 1984,[10] has been a standard therapeutic regimen.

1. Aspirin

In the pre-γ-globulin era, aspirin and corticosteroids were used for the treatment of Kawasaki disease because of their anti-inflammatory effects. Although the therapeutic effects of aspirin in Kawasaki disease are controversial, it remains the drug of choice to be used either as monotherapy or in combination with IVGG therapy.

Both high dose (80 mg/kg or more daily) and moderate dose (30 to 50 mg/kg daily) regimens of aspirin have been used in the acute phase of Kawasaki disease. These regimens, either on their own or in conjunction with IVGG, are associated with a 15 to 25% incidence of coronary artery aneurysm or ectasia[11,12] which is similar to the incidence reported during the natural course of the disease.[13,14] This finding is consistent with prospective studies performed in the γ-globulin era, which showed that aspirin alone was ineffective in reducing the prevalence of coronary artery disease. Aspirin has never been documented in a prospective study to reduce the prevalence of coronary artery abnormalities.

Table I. Diagnostic guideline of Kawasaki disease (reproduced with permission)[4]

This is a disease of unknown aetiology affecting most frequently infants and young children under 5 years of age. The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.

A. Principal symptoms

1. Fever persisting 5 days or more
2. Changes of peripheral extremities: reddening of palms and soles, indurative oedema (initial stage); membranous desquamation from fingertips (convalescent stage)
3. Polymorphous exanthema
4. Bilateral conjunctival congestion
5. Changes of lips and oral cavity: reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
6. Acute nonpurulent cervical lymphadenopathy

At least five of the items numbered 1 to 6 should be satisfied for diagnosis of Kawasaki disease. However, patients with four items of the principal symptoms can be diagnosed as having Kawasaki disease when coronary aneurysm is recognized by two dimensional echocardiography (2-D echo) or coronary angiography.

B. Other significant symptoms or findings

The following symptoms and findings should be clinically considered:

1. Cardiovascular: auscultation (heart murmur, gallop rhythm, distant heart sounds). ECG changes (prolonged PR or QT intervals, abnormal Q wave, arrhythmias), radiographic findings (cardiomegaly), 2-D echo findings (pericardial effusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (auxiliary etc.), angina pectoris or myocardial infarction
2. Gastrointestinal tract: diarrhoea, vomiting, abdominal pain, hydrops of gall bladder, paralytic ileus, mild jaundice, slight increase of serum transaminases
3. Blood: leucocytosis, thrombocytosis, increased erythrocyte sedimentation rate, positive C-reactive protein, hypoalbuminaemia, increased α_2-globulin, slight decrease in erythrocyte and haemoglobin levels
4. Urine: proteinuria, increase of leucocytes in urine sediment
5. Skin: redness and crust at the site of BCG inoculation, small pustules, transverse furrows of the fingernails
6. Respiratory: cough, rhinorrhoea, abnormal shadow on chest radiograph
7. Joints: pain, swelling
8. Neurological: pleocytosis of mononuclear cells in cerebrospinal fluid, convulsion, loss of consciousness, facial palsy, paralysis of the extremities

Remarks

1. For Item 2 under principal symptoms, the convalescent stage is considered important.
2. Male : female ratio: 1.3-1.5 : 1, patients under 5 years of age: 80-55%, fatality rate: 0.3-0.5%
5. Recurrence rate: 2-5%, proportion of sibling cases: 1-2%

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The duration of fever in patients receiving high dose aspirin is shorter than that in patients receiving moderate doses[11,12] although some of the toxic effects of aspirin and complications such as liver dysfunction and gastrointestinal haemorrhage[15-17] have been described, especially with administration of a high dose regimen. A high incidence of liver dysfunction in Japanese patients receiving high dose aspirin suggests racial differences in salicylate sensitivity. Finally, Reye's syndrome has been reported as a rare complication of aspirin therapy for Kawasaki disease.[16,17] In view of the potential risks of high dose aspirin regimens, moderate or low dose aspirin therapy is recommended for the maintenance of an antiplatelet effect. Although no comparison has been performed with other antipyretic agents, alternative antipyretic and anti-inflammatory agents, such as ibuprofen can be used for fever control or severe arthritis.

2. Corticosteroids

As prednisone and related medications are the treatment of choice in other forms of vasculitis, they were widely used in Kawasaki disease in the pre-γ-globulin era in Japan. However, a subgroup of patients was found to be resistant to cortico-

steroid therapy. Most of these patients consequently developed coronary artery aneurysms, many of which were large. Studies by the Japan Kawasaki Disease Research Committee found that coronary abnormalities occur despite corticosteroid treatment in Kawasaki disease.[18] On the other hand, both oral[19,20] and intravenous[21] corticosteroids have been found to effectively prevent coronary artery aneurysms. Corticosteroid therapy of Kawasaki disease therefore remains controversial. Wright et al.[22] suggested that 1 to 3 days of pulsed doses of methylprednisolone (30 mg/kg per day) should be used for patients with IVGG-resistant Kawasaki disease or patients with recrudescent disease after appropriate therapy. Some authors have suggested that corticosteroids are indicated for the treatment of patients with Kawasaki disease who have life-threatening myocarditis, congestive heart failure or severe pericarditis.[23]

3. High Dose Intravenous γ-Globulin

3.1 Mechanism of Action

The mechanism of action of IVGG in Kawasaki disease is unknown. γ-globulin may act by a blockade or modulation of Fc receptors, by providing a specific antibody against an aetiological agent or toxin, by an anti-idiotypic mechanism[24] resulting in suppression of antibody function, or both, or by downregulation of cytokine production. The modulatory effects of immune globulin are not limited to humoral immunity, because cellular immune regulation is also altered during therapy.[25] Microbial toxins such as staphylococcal toxin and streptococcal toxin have been proposed to play an important role in the pathogenesis of Kawasaki disease, by acting as a superantigen that binds nonspecifically to Class 2 major histocompatibility molecules or to certain variable beta regions of the T-cell antigen receptor.[26] Furthermore, the $F(ab)_2$ preparation of pooled immunoglobulin (Ig)G inhibits T-cell activation by staphylococcal enterotoxin B to a similar degree to whole pooled IgG, whereas the Fc fragment of pooled IgG was not inhibitory.[27] This aetiological assumption, however, is not compatible with the description that the biological activity of the Fc region of the γ-globulin molecule plays an important role in its therapeutic effects (section 3.4).

Immune complexes have been isolated from the sera of patients with Kawasaki disease.[28] Competition for the Fc receptors of blood vessels exists between the Fc portions of the complexes and the γ-globulin injected. The possible therapeutic role of immune modulation is consistent with studies in an animal model of arteritis induced by injecting foreign serum as a prototype of the immune complex disease.[29] In this model, high dose γ-globulin-treated animals had less arteritis than control animals.[30] γ-globulin could turn soluble circulatory immune complexes into insoluble ones, which are easily removed by macrophages.

3.2 Clinical Findings

Furusho et al.[10] found that high dose IVGG (400 mg/kg/day for 5 consecutive days) plus aspirin (30 to 50 mg/kg/day until the fever disappeared, then 10 to 30 mg/kg/day) reduced the frequency of coronary artery abnormalities in children to 15.0% (6 out of 40) in the first 30 days after the onset of illness and 2.5% (1 out of 40) in the second 30 days. This was lower than the 42.2% (19 out of 45) and 24.4% (11 out of 45) reported during the same periods in children who received aspirin alone. The study excluded patients with a coronary artery lesion on admission and used unblinded echocardiographic readings and multiple protocol exclusions. The diagnosis of coronary artery abnormalities with echocardiogram should be made under the objective interpretation of independent, blinded readings by several echocardiographers. The results of this study were dependent on the attending physician conducting the evaluation of coronary artery lesions and may have been biased by subjective error. In our multicentre, randomised trial, a discrepancy of reading between the attending physician and several independent echocardiographers was recognised in 20% (95 of 474) of patients with normal or ectasia of coronary arteries.[31]

Based on these observations, Newburger et al.[32] conducted a multicentre, randomised trial in the US. IVGG administered in 4 consecutive daily doses (400 mg/kg/day) together with aspirin resulted in a marked reduction in the prevalence of coronary artery abnormalities as compared with aspirin alone. Each patient's echocardiographic findings were interpreted blindly and independently by 2 paediatric echocardiographers from study centres other than the one at which the patient was enrolled. The aspirin dosage was 100 mg/kg/day through day 15 of the illness, then 3 to 5 mg/kg/day. Two weeks and 7 weeks after enrolment, 8.0% (6 out of 75) and 3.8% (3 out of 79) of the patients in the IVGG group compared with 23.1% (18 out of 78) and 17.7% (14 out of 79) in the aspirin group, respectively, exhibited lesions ($p = 0.01$ and 0.005 by Fisher's exact test).

Children whose enrolment echocardiograms indicated coronary artery abnormalities were excluded. Among the remaining patients, lesions were detected 2 and 7 weeks after enrolment in 6.8% (5 out of 74) and 2.6% (2 out of 77) of patients in the IVGG group compared with 21.3% and 14.7% in the aspirin group (15 and 11 of 75), respectively. Prevalences in the 2 groups by 7 weeks were significantly different ($p = 0.01$). Furthermore, this treatment had a rapid and dramatic anti-inflammatory effect. An aspirin dosage of 100 mg/kg/day demonstrated antipyretic and anti-inflammatory effects but the reduced dosage of 30 to 50 mg/kg/day (to prevent severe hepatic dysfunction) may be insufficient to produce these actions.

3.3 Dosage

The results of multicentre, randomised trials performed by the Research Committee of Health and Welfare Ministry of Japan on Kawasaki disease[33] which compared the efficacies of IVGG 100mg and 400mg suggest that the dosage of γ-globulin is an important determinant of its efficacy. However, the high cost of IVGG as well as the possibility that immune responses are activated by high dose administration and that some infectious agents are contained in the preparations make the determination of an optimal dose a very important issue.

In a randomised, controlled study of children considered to be at high risk for coronary artery abnormalities, the severity of coronary artery lesions was greater among those who received IVGG 200 mg/kg/day for 5 days than those who received 400 mg/kg/day for 5 days.[34] Furthermore, a Japanese multicentre, controlled trial conducted by Osaka Kawasaki Disease Research Group compared the outcome in 84 patients with Kawasaki disease who were randomly assigned to treatment with either IVGG 1 g/kg and aspirin or aspirin alone. No difference in the prevalence of coronary lesions was found between the groups.[35] However, the same research group found that IVGG 400 mg/kg/day for 3 consecutive days plus aspirin significantly reduced the prevalence of coronary artery lesions, as compared with aspirin alone.[36] These studies suggest that a total dose more than 1g per kilogram is effective.

Motivated by the potential economic and social benefits of shortening the hospital stay for patients with Kawasaki disease, Newburger et al.[37] conducted a second multicentre, randomised trial to ascertain whether the IVGG in a single infusion of 2 g/kg over 10 hours would demonstrate similar or better efficiency than daily infusion of 400 mg/kg for 4 consecutive days. Both treatment groups received aspirin in the same regimen as the first trial.[32] They found that a single large dose of IVGG (2 g/kg) was more effective than the conventional regimen of 4 smaller daily doses (a total of 1.6 g/kg) and is equally well tolerated. However, the efficacy of a single large dose was not explained by serum IgG levels which did not differ significantly between the groups at day 4 and week 2. Moreover, the investigators found an association between low peak IgG levels and a poor outcome and suggested that a relationship exists between the serum IgG concentration and therapeutic effectiveness, regardless of a single large dose or divided daily doses for consecutive days. We found the serum IgG level of a single large dose higher

than the regimen of 5 smaller daily doses until day 4, especially on day 2.[38]

The temperature in some patients treated with a conventional regimen of successive daily doses fell before the total dose was administered. To determine the optimal dose, a survey by the Research Committee on Kawasaki Disease, Japan Ministry of Health and Welfare reported that the best regimen may be an initial dose of more than 1 g/kg followed by an additional dose if the fever continues for 2 days.[39]

A small but significant group of children with Kawasaki disease did not respond fully to treatment with a standard dose. With standard IVGG regimens, fever persisted or recurred within several days of completing the initial course of therapy.[37] In such cases, readministration of 1 g/kg (once to several times) has been recommended.[40,41] However, repeat treatment with a single infusion of IVGG 2 g/kg may be preferred in these patients because it reduces the need for two repeat treatments. When γ-globulin treatment is repeated, the serum IgG level may indicate a single large dose rather than smaller daily doses. Suto et al.[42] described a child with Kawasaki disease in whom IVGG 330 mg/kg/day for 11 consecutive days had no effect and resulted in a serum IgG level of 28.55 g/L, the same as the level on day 5. γ-globulin 2 g/kg at day 12 immediately normalised temperatures and increased the serum IgG level to 33.82 g/L.[42] No trials comparing additional doses of 1 g/kg and 2 g/kg have been reported.

3.4 Different Efficacies of Various Formulae

As the mechanism of action of IVGG is unknown, standardisation of IVGG preparations is not possible. It is unclear whether all commercially available IVGG preparations or various batches of the same preparation are equally effective. IVGG preparations are classified into 3 main categories: enzymatically treated formulations, chemically modified formulations and native IgG preparations. Enzymatically treated formulations have been found to have no effect in improving Kawasaki disease vasculitis as confirmed by the Kawasaki Disease Research Committee, Ministry of Health and Welfare of Japan in a clinical trial (aspirin alone *vs* pepsin-treated γ-globulin *vs* whole molecule: sulfonated γ-globulin or polyethylene glycol-treated γ-globulin).[43]

Based on the observation that a total dose more than 1 g/kg is effective, Onouchi et al.[44] conducted a multicentre, randomised trial of aspirin *vs* 2 different dosages of reduced and alkylated γ-globulin (200 mg/kg/day and 400 mg/kg/day for 5 consecutive days) together with aspirin (50 mg/kg/ day until the fever disappeared, then 30 mg/kg/day).[44] While dose-dependent inhibition of coronary artery lesions was observed in the γ-globulin groups, the outcome in 85 patients revealed no significant differences among the 3 groups. Determining the efficacy of alkylated γ-globulin may therefore require examination of a larger number of patients. On the other hand, reduction and alkylation of the s-s bond in the hinge region of the γ-globulin molecule has been shown to affect complement binding in the classical pathway.[45] Moreover, the Fc region altered by reduction and alkylation is considered to have a deleterious effect on immune complex formation.[46] Comparing the opsonisation effects of alkylated γ-globulin and native γ-globulin derived from the same plasma (sibling lots), the *in vitro* opsonisation activity of alkylated γ-globulin was lower.[47] This finding suggests that the affinity of reduced and alkylated γ-globulin for Fc receptors on various cells is diminished.

Sulfonated γ-globulin which is similarly chemically-modified revealed superior effects at the dosages of 400 mg/kg/day for 3[36] or 5[10] consecutive days to aspirin alone. This finding does not support our results with alkylated γ-globulin and suggests that the sulfonate group separates from the molecule within 24 hours of entering the biosystem, thus leaving native IgG.[48] Therefore, the contrasting results among enzymatically treated formulations, chemically modified formulations and native IgG preparations suggest that biological activity of the Fc region of the γ-globulin molecule has a major effect on its efficacy in improving Kawasaki disease vasculitis.

Two Japanese multicentre, controlled trials (with objective interpretation of independent, blinded readings by several echocardiographers) conducted by Morikawa et al.[49] and Onouchi et al.[50] found that the native IgG preparations polyethylene glycol-treated γ-globulin and pH4 stabilised acid γ-globulin (400 mg/kg/day for 5 consecutive days in combination with aspirin 30 mg/kg/day) are the most effective agents. Patients in both trials showed no coronary artery lesions before IVGG therapy. In the former trial in 451 patients treated for 5 consecutive days, the incidence of coronary artery lesions after 30 days of illness was 12.9% in patients receiving polyethylene glycol-treated γ-globulin 200 mg/kg/day, 4.6% in those receiving polyethylene glycol-treated γ-globulin 400 mg/kg/day, and 17.7% in those receiving sulfonated γ-globulin 200 mg/kg/ day. The between-group difference in this trial[49] was highly significant. In the latter trial, on the other hand, the incidence of coronary artery lesions in 142 patients who received pH4 stabilised acid γ-globulin on day 15 were 26.7, 12.2 and 3.8% in the 100mg, 200mg and 400mg dose groups, respectively. Corresponding results on day 30 were 11.4, 4.5 and 2.0% and on day 60 were 6.8, 2.3 and 1.9%. There was a significant difference between the 100mg and 400mg group in the incidence of coronary artery lesions on the 15th day, while dose-dependent inhibition of coronary artery lesions was observed at all times. IVGG used in the trial of Newburger et al. described previously[32] was also polyethylene glycol-treated γ-globulin, Immuno AG (Vienus, Austria).

3.5 Tolerability

γ-globulin is a biological product made from pooled donor plasma. γ-globulins available for use in most countries are associated with no discernible risk of hepatitis or HIV infection, but may contain some infectious agents. Recently, parvovirus 19 was found in preparations of plasma fractionation.[51]

However, the use of IVGG has been associated with markedly few adverse effects. Minor adverse reactions, such as fever, chills, flushing, and rashes occur in fewer than 8% of patients.[52] Polyethylene glycol treatment of γ-globulin eliminates a polymer and is therefore expected to prevent adverse events associated with polymers, such as anaphylaxis.[53] Because of the remaining polymer, however, a trial using polyethylene glycol-treated immunoglobulin revealed a rare but significant incidence of anaphylactic shock.[49] Rarely, serum sickness or aseptic meningitis may follow IVGG infusion.[54]

Treatment with high dose intravenous γ-globulin may induce thrombotic events in patients with hypercoagulability or a tendency toward thrombus formation.[55] Severe anaphylactoid reactions may occur in IgA-deficient people.[56]

3.6 Indication

IVGG treatment is expensive and not completely without risks. Furthermore, whether or not it should be reserved for a subgroup of patients with severe Kawasaki disease has not been determined. Several adverse prognostic features have been recognised including prolonged fever, severe anaemia, hypoalbuminaemia, leucocytosis and extreme thrombocytosis. None of these features is specific for the identification of at-risk patients and most researchers in the US and European countries therefore currently advocate administering IVGG to all patients with Kawasaki disease. In Japan, however, some centres only treat children predicted to be at high risk of coronary artery disease,[57] as evaluated by Harada's score.[58]

IVGG, other drugs, hospitalisation, clinic visits and laboratory costs differ between countries. Within the US healthcare system, treatment with a single high dose of IVGG 2 g/kg was estimated to cost less than aspirin alone or 4 days treatment with low dose IVGG 400 mg/kg/day.[7]

4. Cardiac Transplantation

Cardiac transplantation[14] is indicated for a small population of patients with acute phase Kawasaki disease. There are at least 2 potential indications for cardiac transplantation in Kawasaki disease. The first is the presence of severely impaired

left ventricular function secondary to myocardial infarction and severely damaged myocardium. The second indication is extensive distal coronary disease that makes successful bypass grafting technically impossible in a patient at risk for severe myocardial infarction or sudden death from ventricular arrhythmias.

5. Conclusion

IVGG treatment of Kawasaki disease significantly reduces the duration of fever, systemic inflammation, and prevalence of coronary artery lesions. Today, high dose IVGG therapy combined with aspirin is the standard modality of treatment in Kawasaki disease. Recommended dosages of aspirin vary from 30 to 100 mg/kg/day in the acute phase reduced to an antiplatelet dose of 2 to 5 mg/kg/day once the fever has declined.

In cases of persistent fever or recurrence with standard IVGG regimens, readministration of IVGG 1 g/kg (once to several times) should be considered.

Some patients with relatively low levels of C-reactive protein may be treated with a conventional regimen of successive daily doses of 400 mg/kg/day until the temperature falls. However, the mechanism of action of IVGG in Kawasaki disease remains to be clarified.

Mild cases of Kawasaki disease may be treated with aspirin alone (30 to 100 mg/kg/day in the acute phase reduced to 2 to 5 mg/kg/day once the fever has declined).

Many centres prescribe dipyridamole in a dose of 5 mg/kg/day as an additional antiplatelet agent and warfarin 0.1 mg/kg/day, not to exceed 10 mg/day on a loading dose for 3 to 5 days. Monitoring is conducted with the one-stage prothrombin time to prolonging the value 1.5 to 2 times the baseline value. Warfarin 0.05 mg/kg/day can be used as a maintenance dosage for anticoagulation in patients with detectable giant aneurysms.

Importantly, the agent(s) involved in the pathogenesis of Kawasaki disease must be identified in order to establish more specific therapies.

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