Pediatric rheumatology

Sequential changes to clinical parameters and adhesion molecules following intravenous pulse cyclophosphamide and methylprednisolone treatment of refractory juvenile idiopathic arthritis

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Abstract

It is believed that the systemic subtype and the positive rheumatoid factor, polyarticular subtype of juvenile idiopathic arthritis (JIA) show the least favorable outcomes for therapy; patients with systemic JIA are often resistant to recommended therapeutic modalities.

We report the sequential changes to clinical and laboratory findings from pulse therapy with monthly intravenous cyclophosphamide (0.5 g/m^2 body surface area) administration combined with methylprednisolone (30 mg/kg; 1 gm maximum) for 6 months, following which the medication interval was elongated to 3 months for a total of from 7 to 12 courses.

Among 4 children suffering from refractory systemic JIA, 3 demonstrated clinical improvement, 2 of whom achieved clinical remission. Furthermore, we also adminstered this therapy to a girl suffering from refractory polyarticular JIA, following which she revealed clinical remission subsequent to 9 courses of such therapy.

From our experience, we suggest that patients afflicted with JIA that is unresponsive to traditional medication may experience benefit from this type of pulse therapy.

Key words

Juvenile idiopathic arthritis, pulse therapy, adhesion molecules, cyclophosphamide, methylprednisolone.

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Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases amongst children, it being characterized by an idiopathic synovitis of the peripheral joints associated with soft-tissue swelling and effusion. The traditional "pyramid" of the routine pharmacological treatment for children suffering from JIA suggests that such therapy commences with NSAIDs, followed by disease-modifying anti-rheumatic drugs (DMARDS) including methotrexate, sulfasalazine, hydroxychloroquine, D-penicillamine, and gold compounds (1). Although methotrexate has been shown to slow radiographic progression for JIA sufferers, and has been reported to be effective for treating oligo- and poly-articular patients, patients with the systemic subtype may respond less frequently (2, 3). Similarly, some studies suggest that systemic JIA responds poorly to sulfasalazine and other DMARDS (4-7).

Oral corticosteroids exhibit potent anti-inflammatory effects, but produce many undesirable side effects subsequent to prolonged use. Cyclosporine appears to be mainly efficacious for the control of fever and the reduction of steroid therapy; although such efficaciousness appears to be less clear-cut with respect to arthritis, laboratory parameters and uveitis (8).

The clinical use of intravenous pulse methylprednisolone (IVMP) has been reported with good results for a large variety of autoimmune disorders (9-12). When applied to juvenile arthritis, Adabajo *et al.* reported that IVMP might provide notable benefit for patients suffering from systemic JIA(13). The administration of cyclophosphamide in a periodic bolus form appears to elicit a more profound effect and less toxicity compared with the daily oral form in the treatment of SLE (14, 15). It has been also shown to be effective for the treatment of other autoimmune diseases (16, 17).

The development of a pharmaceutical regimen using a combination of intravenous pulse cyclophosphamide (IVCY) plus IVMP was based upon a number of successful treatments for patients suffering severe autoimmune diseases (18, 19). With regard to JIA patients, Shaikov *et al*. (20) reported a rapid and significant suppression of the systemic and articular manifestations of systemic JIA amongst patients subsequent to IVCYand IVMP therapy. Wallace *et al*. (21) reported that 3 of 4 systemic JIA patients achieved remission from their disease and all of them showed an increase in linear growth following their treatment.

This inflammatory process of JIA is generated by a series of events, including the migration of leukocytes from the bloodstream into the tissue, their activation to become effector cells, and finally their local retention to facilitate the ongoing immune reaction (2). Adhesion molecules play a part in all of these phases and have a major role in the disease process. In our previous study we reported significantly higher levels of soluble intercellular adhesion molecule-1 (sICAM-1) in patients with active JIA than for those in remission and normal controls (22). In this report, we evaluated the sequential changes to clinical and laboratory parameters, including the erythrocyte sediment rate (ESR) and soluble intercellular adhesion molecule-1 (sICAM-1) levels during and following IVCY and IVMP treatment in 5 JIApatients who were refractory to previous therapeutic regimes.

Diagnosis and treatment of the patients

Four children afflicted with systemic and one suffering from polyarticular JIA who had been treated consecutively at the rheumatology clinic of Chang Gung Children's Hospital were subsequently treated using IVCY and IVMP therapies. These patients fulfilled the classification criteria for JIA (23). The initial systemic signs exhibited by the 4 children included fever, serositis, hepatosplenomegaly, and/or evanescent skin rashes that were classic for systemic JIA. The duration of these various diseases prior to treatment with IVCY ranged from 14 to 42 months and the symptoms had all proven refractory to previous medication regimes (Table I). The medication used in all cases was intravenous cyclophosphamide (0.5 g/

Table I. Characteristics of the 5 JIApatients who received IVCYand IVMPtherapy. Patients nos. 1 to 4 had systemic JIAwhile patient no. 5 was suffering from polyarticular JIA.

Pt. no.	Age[1]/ sex	Disease duration	Clinical manifestations prior to pulse therapy	Medication before IVCY& IVMP	IVCY & IVMP courses	Status after therapy	Prednisolone dose[2] (mg/kg/day) Before	After
1	6/M	14 mo.	Fever, left knee arthritis	NSAID, Pred, CS	8	Improved	0.6	0.17
2	12/M	31 mo.	Bilateral wrists and right knee arthritis	NSAID, Pred, MTX	8	Remission	0.5	0
3	9/M	42 mo.	Fever, multiple joints swelling and deformity	NSAID, Pred, CS	7	Not improved	0.5	0.2
4	14/F	15 mo.	Fever, multiple joints swelling	NSAID, Pred, MTX, CS	12	Remission	0.28	0.06
5	14/F	23 mo.	Right knee, ankle, and left elbow swelling	NSAID, Pred, MTX, CS	9	Remission	0.35	0

[1]Age in years; [2]prednisolone dose before and after therapy.
NSAID: non-steroid anti-inflammatory drugs; Pred.: prednisolone; MTX: methotrexate; CS: cyclosporine.

m^2 body surface area) and methylprednisolone (30 mg/kg; 1 gm maximum). Patients were admitted to hospital for a single dose of IVCY, and a single dose of IVMP was given 4 hours subsequent to the completion of the initial IVCY therapy. Each patient received 6 monthly treatments, and additional treatments were given subsequently every 3 months for a total of from 7 to 12 courses. Informed consent to participate in this investigation was obtained from each patient's parents or guardians prior to commencement of this study.

All patients were followed up monthly, with their clinical manifestations examined in close detail, including the number and range of motion of involved joints, the severity of joint tenderness, the duration of morning stiffness, and the side effects of any medication given. Laboratory studies including a complete blood count (CBC), ESR, and a full blood biochemistry assay were checked uniformly one month following the administration of IVCY and IVMP. From each blood sampling, a tube of frozen serum was specially preserved for further study of the soluble intercellular adhesion molecule-1 (s-ICAM-1). Patients were considered to have achieved clinical remission when they experienced morning stiffness that did not exceed 15 minutes duration, and reported no fatigue, joint pain, joint tenderness, or joint or tendon-sheath swelling, and an ESR < 20 mm/hr (based on the ACR criteria for remission of adult rheumatoid arthritis) (24).

Patient 1

The patient, an 8-year-old boy, presented with a 3-week history of fever; lethargy; rash on his face, trunk, and pretibial area; and arthralgia on both knees. Pericardial effusion, 8 mm in thickness, was determined by cardiac 2-D echo at the time of examination.

The initial treatment included NSAIDs combined with prednisolone, and following this cyclosporine was added some 2.5 months later. The pericardial effusion disappeared within a period of 3 months, but recurrent arthritis in both knees and relapsing fever continued to trouble this patient. Although naproxen, oral prednisolone and cyclosporine was administered, the arthritis and fever persisted.

The treatment was amended to IVCY plus IVMP, and the clinical manifestations and associated laboratory abnormalities in the patient improved gradually. At the time of the 5th course of therapy, a flare of the disease occurred with an associated elevated white blood cell count (WBC: 25,300/mm^3), platelet count (PLT: 647,000/mm^3) and ESR 152mm/hr, fever and left knee arthritis. The patient continued to receive IVCY and IVMPtherapy subsequently. At the end of the 8th course of therapy, all the clinical manifestations had subsided apart from a mildly elevated PLT of 400,000/mm^3 and an ESR of 62mm/hr. The serum ICAM-1 level was also observed to fluctuate, reaching a lower level after 8 courses of therapy (Table I and Fig. 1).

Patient 2

This 12-year-old boy demonstrated a one-month history of relapsing fever, hepatomegaly, and right knee swelling, and upon presentation systemic JIA was diagnosed. The patient was treated with NSAIDs and prednisolone, with methotrexate being added to the therapeutic regime some 3 months later. The arthritis, however, spread bilaterally to the wrists and ankles, and also to the right knee. Other medication such as cyclosporine had been tried in this patient, although his body weight and height were less than the fifth percentile for age-matched children due to his fluctuating and prolonged illness.

Treatment with IVCY and IVMP was started about 2.5 years subsequent to the diagnosis of this patient's condition, following which his clinical manifestations improved gradually. The laboratory data returned to normal following 4 courses of IVCY treatment. After 7 courses had been completed the patient achieved clinical remission and NSAIDs alone were prescribed for him. The improvement in hemoglobin level was very significant for this patient (pre-treatment: 7.1, post-treatment: 12.4 mg/ dL), but little improvement in sICAM-1 was noted (pre: 591.8, post: 618.4 ng/ mL; Table I and Fig. 1).

Patient 3

This patient, a 9-year-old male and a carrier of α-thalassemia, presented with a 3-month history of intermittent fever

and subsequent right knee swelling for the previous one month. He was diagnosed with JIA, and treated for 9 months with prednisolone and NSAIDs. During the follow-up, however, the fever was still apparent, albeit intermittently, associated with multiple joint swelling and deformity. X-ray examination revealed bilateral carpal-bone erosions, as a result of which cyclosporine was added to the therapeutic protocol, although the patient's condition did not improve dramatically, and his existing anemia worsened (Hb: 5.7 mg/dL).

We started IVCYand IVMPtherapy 42 months subsequent to the initial diagnosis. Following 7 courses of treatment, his clinical manifestations – including fever, maculopapular rashes, and arthralgia – still occurred, albeit occasionally. Comparing the laboratory findings prior and subsequent to the commencement of IVCY and IVMP therapy, whilst the patient's hemoglobin level did improve (8.5 mg/dL from an original 5.7 mg/dL), other laboratory abnormalities including leukoctyosis (WBC: 19,500/mm^3), thrombocytosis (PLT: 631,000/mm^3), an elevated ESR (74mm/hr) and an elevated sICAM-1 level (pre: 974.9, post: 1,055.7 ng/mL) revealed a rather poor response to the therapeutic regimen. Due to the patient's prolonged illness, he presented growth retardation and a limping gait (Table I and Fig. 1).

Patient 4

This 14-year-old female was diagnosed as having systemic JIA4 years prior to the preparation of this manuscript, revealing a 1-month history of relapsing fever, left knee arthritis, and skin rashes over her face, trunk, and extremities. She was initially treated with NSAIDs and prednisolone, and had once been admitted for the administration of intravenous immunoglobulin due to her poor response to methotrexate therapy, although even following this therapy the patient's symptoms of fever and joint swelling still occurred intermittently.

Fifteen months subsequent to the onset of her disease, she was placed on IVCY and IVMP therapy, and a total of 12 courses of treatment were completed during this period. Following this, she achieved clinical remission, although our additional laboratory investigation of sICAM-1 levels revealed little improvement from her original condition (pre: 2,468.6, post: 1,845.2 ng/ml). Unfortunately, because of the complications of muscular atrophy of the right thigh and avascular necrosis of the right femoral head, she was referred to our orthopedic department for subsequent hip-joint replacement (Table I and Fig. 1).

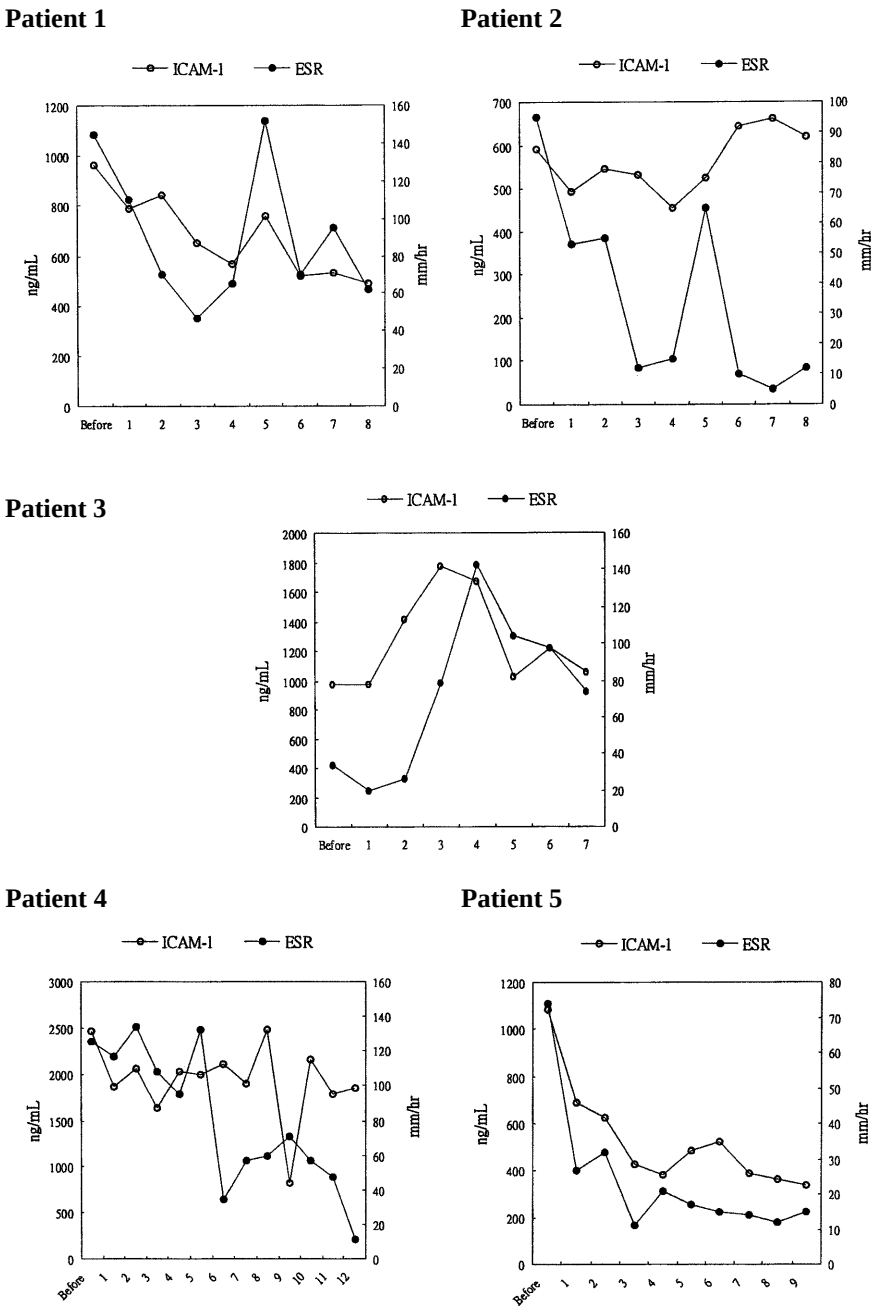

Fig. 1. The serial changes to sICAM-1 and ESRlevels during the treatment courses of IVCY and IVMPfor patients nos. 1 to 5.

Patient 5

This patient, a 15-year-old girl, presented with a 2-month history of swelling and tenderness in multiple joints, including the MP joints of both feet, her left elbow, and her right ankle. She was referred to our unit from the orthopedic clinic due to a poor response to 3 weeks of therapy with NSAIDs. The patient's medication was adjusted progressively subsequent to a diagnosis of polyarticular JIA having been made.

About 1.5 years subsequent to this, her medication included NSAIDs, prednisolone, cyclosporine, and methotrexate, although morning stiffness and painful, swollen joints appeared occasionally without any apparent deformity or disability. The patient missed a large number of school days and was clearly psychologically depressed.

Two years after the onset of JIA, she was treated with IVCY and IVMP, and achieved clinical remission following 8 courses of therapy. The patient's serum ICAM-1 level declined markedly (pre: 1,084.2, post: 338.0 ng/mL) (Table I and Fig. 1).

Side effects

None of our patients suffered from hemorrhagic cystitis, but a number of side effects attributable to the IVCY and IVMP medication were observed during the course of the therapy. Two of the 5 patients developed vomiting, and 2 experienced a prolonged bad taste during therapy. None of the patients revealed any evidence of any unstable vital signs during the course of therapy. One revealed mild alopecia and one complained of rapidly increasing body weight.

Discussion

The mechanisms of intravenous megapulse injection of corticosteroids for patients afflicted with arthritis have been widely discussed, and it would appear that the presence of a variety of adhesion molecules may be affected. IVMP has been shown to elicit a rapid decrease in the expression of E-selectin and ICAM-1 in the synovial membrane (25), and a marked decrease in CD11b and CD18 expression from synovial neutrophils (26).

Cyclophosphamide depresses delayed-type hypersensitivity more substantially than humoral immunity following long-term therapy, whereas pulse therapy or high-dose cyclophosphamide mainly disrupts humoral immunity (27). When both intravenous cyclophosphamide and methylprednisolone therapies are combined for adult patients suffering from rheumatoid arthritis, a number of studies have indicated that a decrease in total lymphocyte count, NK cells, and activated T cells is likely to be observed (28). Similar results may occur in children treated similarly, and these mechanisms could help in reducing the inflammatory response of refractory JIApatients.

Our results have revealed that of the 4 systemic JIA patients treated with IVCY and IVMP, 2 achieved clinical remission following 8 and 12 courses of therapy, respectively, one experienced an improvement from the earlier disease activity and one patient's therapy was still in progress. Wallace *et al*. (21) have reported that 3 out of 4 four systemic JIA patients achieved clinical remission after between 12 and 20 courses of treatment. The differences in remission rate between these two studies are probably due to the greater number of courses of pulse therapy and also the weekly methotrexate therapy administered concomitantly in the study of Wallace. The possibility remains that the remission rate would have been higher for the patients participating in our study if a greater number of courses of pulse therapy were administered.

In patient no. 2 and patient no. 4 we noted the additional finding that, despite the (apparent) remission status of the systemic JIA, the serum levels of soluble intercellular adhesion molecule-1 (sICAM-1) remained elevated. This finding was compatible with our previous report (22), which noted that despite the apparent remission status of the three subtypes of JIA, the soluble adhesion molecules were still significantly elevated compared with the normal control groups, and this probably helped to explain the fluctuating activity and frequent recurrence of JIA, as a result of leukocyte-endothelium interaction and resulted in joint inflammation and destruction.

The single case of polyarticular JIA in our study, patient no. 5, appeared to respond well to pulse therapy. This particular patient reached normal levels as regards laboratory parameters subsequent to 4 courses of pulse therapy and achieved clinical remission status following the 7th course of therapy. Due to the very limited number of cases involved in this study, no firm conclusions should be drawn, although it would be fair to say that that the laboratory parameters suggest that polyarticular JIA shows a better therapeutic response to IVCYand IVMP therapy because it is clinically a less severe condition than systemic JIA. Thus our patient (no. 5) responded quickly without subsequent response fluctuation or flaring. When compared with the other systemic JIA patients, she achieved clinical remission with a progressively decreasing sICAM-1 level.

In terms of the involvement of adhesion molecules in JIA, we are confident that systemic JIA is associated with a greater mortality and morbidity than its polyarticular subtype, and that the probability of a flare of the disease in patients nos. 2 and 4 was higher than was the case for patient no. 5, although all 3 of these patients did achieve clinical remission.

The only apparently inconsistent result in our study was patient no. 3, who appeared to be unresponsive to the IVCY plus IVMP therapy. As we mentioned above, this patient could very well benefit from further courses of therapy or other new remedies such as autologous stem-cell transplantation. IVCY plus IVMP remains a safe therapeutic modality, effective, and worthy of recommendation to refractory JIApatients.

Most of the side effects observed with the administration of IVCY and IVMP were infrequent and mild; our patients were able to tolerate them easily. The issue of the risk of late complications associated with the administration of cyclophosphamide, e.g. gonad failure and malignancy, however, were difficult to address in our children. Whilst patient no. 4 did experience substantial improvement as regards the severity of her disease, she finally developed avascular necrosis of the right femoral head. However, she had taken oral corticosteroids for a period of 5 years prior to the detection of her avascular necrosis, so it would seem appear to attribute this necrosis to the IVMPtherapy.

In recent years, etanercept has been approved for the treatment of polyarticular JIA(29). Lovell *et al.* tested etanercept in a group of 69 patients suffering from polyarticular JIA, and reported significant improvement in patients'

condition with a good tolerance of the medication (30), although some questions do remain unsolved, such as whether etanercept administration can be generalized for all subtypes of JIA, and what the long-term efficacy and safety profile will be for etanercept used alone or in combination with DMARDs for the treatment of JIA(31).

Another newly developed treatment, autologous stem-cell transplantation (ASCT), was first reported in 1999, Wulffraat *et al*. reporting that ASCT elicited a striking effect upon refractory JIA patients, the therapy revealing drug-free improvement (32). More recently a multi-center study has revealed that although the complete remission rate for JIA patients so treated did exceed 50%, it should also be recognized that the ASCT-related mortality ranged from 5 to 12%. Clearly therefore the appropriate selection of patients for such a therapeutic modality remains critical, and further randomized trials of ASCT therapy are necessary (33).

In summary, we offer this report to highlight our experience with treating JIA patients refractory to traditionally recommended medications. Four of our 5 patients demonstrated a clear improvement to their condition and 3 of them achieved clinical remission. The combination of IVCY plus IVMP therapy was associated with minor and well-tolerated side effects in our patients, apart from one subject who developed avascular necrosis of the femoral head. We suggest that JIA patients who suffer from severe complications or are refractory to traditional therapeutic regimes may benefit from the administration of this therapeutic modality.

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