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SHORT COMMUNICATION

Clarithromycin in adult-onset Still's disease: a study of 6 cases

Gianantonio Saviola · Maurizio Benucci · Lul Abdi-Ali · Paola Baiardi · Mariangela Manfredi · Mariarosaria Bucci · Giuseppe Cirino

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Abstract Adult-onset Still's disease (AOSD) is a rare rheumatological condition characterized by an acute systemic involvement. There are no treatment guidelines. Glucocorticoids (GC), methotrexate (MTX), cyclosporin A and biologic agents have been successfully used, often in association. We treated six cases of AOSD with clarithromycin (CM) in combination with low-mild dose of GC and MTX. Four of them were not responsive to high-dose GC added to DMARDs, while two of them were treated with low-mild dose of GC added to CM from the beginning. CM, 500 mg b.i.d., was added to a mild-low dose of GC and to MTX. The dose of the drugs was reduced (and stopped where possible) following clinical and laboratory parameters. ACR criteria were used to assess clinical improvement. At 6 months 5 patients reached ACR 70% and could stop any therapy in 6–18 months; 1 continued chronic therapy with low-dose GC added to CM and MTX to maintain ACR 50%. CM can be a useful drug for the treatment of AOSD, even in patients not responsive to high-dose GC and DMARDs. No definitive conclusion can be drawn based on the present study.

Keywords AOSD · Adult-onset Still's disease · Rheumatic disease · Clarithromycin · Macrolide antibiotics

Abbreviations

AOSD	Adult-onset Still's disease
CM	Clarithromycin
CRP	C-reactive protein
CP	Cyclophosphamide
CsA	Cyclosporin A
DMARD	Disease-modifying antirheumatic drug
SSZ	Sulfasalazine
ESR	Erythrocyte sedimentation rate
GC	Glucocorticoids
HCQ	Hydroxychloroquine
LDH	Lactic dehydrogenase
MTX	Methotrexate
MP	Methylprednisolone
NSAID	Non-steroidal anti-inflammatory drug
RA	Rheumatoid arthritis
α-TNF	α-Tumor necrosis factor
UCTD	Undifferentiated connective tissue disease
WBC	White blood cell
PLA2	Soluble type II phospholipase A2
PGE2	Prostaglandin E2
ivIg	Intravenous polyvalent immunoglobulin
Col	Colchicine
MMF	Mycophenolate mofetil
AZA	Azathioprine

G. Saviola (✉) · L. Abdi-Ali
Rheumatology and Rehabilitation Unit,
Salvatore Maugeri Foundation IRCCS,
Castel Goffredo, Mantua 46042, Italy
e-mail: gianantonio.saviola@fsm.it

M. Benucci
Rheumatology Unit, New Hospital S. Giovanni di Dio,
ASL 10, Florence, Italy

P. Baiardi
Methodology Unit, Consorzio Valutazioni Biologiche e
Farmacologiche, Salvatore Maugeri Foundation
IRCCS and University of Pavia, Pavia, Italy

M. Manfredi
Immunology and Allergology Laboratory Unit,
New Hospital S. Giovanni di Dio, ASL 10, Florence, Italy

M. Bucci · G. Cirino
Department of Experimental Pharmacology,
Faculty of Pharmacy, University of Naples–Federico II,
Naples, Italy

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic condition of unknown origin. It is a worldwide reported heterogeneous disease, predominantly affecting young adults (peak age 16–35), characterized by a sudden onset of high spiking fever, which often follows a transient pharyngitis or a maculopapular rush, with a disabling arthritis or arthralgia. Other common symptoms are: sore throat, lymphoadenopathy, hepatosplenomegaly and pericarditis or pleuritis. Laboratory abnormalities include marked leukocytosis with neutrophilia, high level of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactic dehydrogenase (LDH) and liver function tests [1]. However, a pronounced increase in serum ferritin and interleukin-18 levels are probably the most characteristic tests and glycosylated ferritin has been recently purposed as a helpful marker of hemophagocytic syndrome [2].

Preliminary criteria for classification of AOSD have been purposed by Yamaguchi in 1992 consisting in fever, arthralgia, typical rash and leukocytosis as major, and sore throat, lymphoadenopathy and/or splenomegaly, liver dysfunction and the absence of rheumatoid factor and antinuclear antibody as minor criteria. The diagnosis requires the presence of five or more criteria including two or more major criteria [3].

Because of its low prevalence and its heterogeneous expression, the treatment of AOSD has no guideline. The management is first directed at the acute systemic symptoms. NSAIDs have been used with scarce efficacy; while GCs give clinical response in 76–95% of patients [4]. However, other treatments in association with GCs or alone are often needed. By homology with rheumatoid arthritis gold salt, HCQ, D-penicillamine, sulfasalazine (SSZ), cyclophosphamide (CP) were tested, but only cyclosporin A (CsA) [5] and methotrexate (MTX) seem to be really effective [6] with a GCs sparing effect. Moreover polyvalent intravenous immunoglobulin [7] have been successfully tested in patients with AOSD refractory to GCs. Concerning the pathogenesis of the disease, recent studies have suggested an important role for interleukin 1 (IL-1), IL-6, IL-18, macrophage colony-stimulating factor, interferon gamma and tumor necrosis factor (TNF) [8]. For this reason also anti-TNF-α agents have been used showing that these drugs may be helpful in some AOSD patient, but most of them achieved only partial remission [4, 9, 10]. On the other hand, patients with treatment-resistant AOSD have been successfully treated with anakinra, with reduction of IL-18 serum levels [11].

In 2004 a case of refractory AOSD successfully treated with CM was reported [12]. The anti-inflammatory action of CM is well known [13]. A pilot study on the use of CM in RA was published in 2002; 18 RA patients unresponsive to DMARDs were treated with CM for 6 months with successful results in 10 of them [14]. CM showed a very rapid onset of action (10 days) and lowered the plasma levels of PLA2 and PGE2. More recently, Ogrendik [15] confirmed the efficacy of CM in a double-blind trial versus placebo in 81 RA patients obtaining a significant improvement following ACR criteria. In 2006 Moskowitz [16] published a report of seven patients affected by undifferentiated connective tissues disease (UCTD) successfully treated with CM in a 12-week open-label study; he also confirmed the very rapid onset of action (as early as 1 week).

Methods

Here we report six cases of AOSD, diagnosed following the criteria of Yamaguchi [3] and treated with CM. Clinical improvement in disease activity were defined according to the ACR criteria for RA. Side effects either suspected or certain were noted. Therapy was as follows: at the start of the study, 500 mg of CM was administered orally b.i.d., it was then reduced and later stopped following clinical and laboratory parameters. Methylprednisolone (MP) was used at mild-low doses (4–16 mg daily), and was then reduced and stopped whenever possible. MTX at the weekly dose of 15 mg was added in 4 patients while 2 patients (young females) refused it because of its teratogenicity. All the patients gave their informed consent to the treatment according to the Declaration of Helsinki.

Results

All six patients followed Yamaguchi diagnostic criteria for AOSD. Baseline characteristics are shown in Table 1.

Mean age of patients was 36 ± 4.65 years.

Median duration of the disease was 6 months (3–200 months). In four patients this was the first attack of the disease. In patient no. 2 this was his fourth attack, while in patient no. 6 this was her third attack.

Following ACR criteria six patients reached an ACR 50% improvement at 6 months, five patients an ACR 70% improvement. Outcomes are shown in Table 2.

Side effects were: (1) elevated hepatic enzymes in Case 1, due to MTX, that was stopped; (2) nausea in Case 2, due to MTX, that was stopped; (3) metallic taste in five patients. Only patient no. 5, even in partial remission (ACR 50%), decided to stop CM because of this side effect. This decision caused a flare (ACR < 20%) in 10 days not controlled by other DMARDs or by increasing GC dose. Consequently, patient no. 5 decided to continue with CM reaching again the ACR 50% improvement in a short time.

Table 1 Baseline characteristics of the patients

Case	Sex	Age	Ferritin (ng/ml) (n.v. < 150)	ESR (mm/h)	Fever	Arthralgias or arthritis	Rash	WBC × 10^3/μL (polynuclear > 75%)	RF	ANA	Sore throat	Lymphadenopathy/ splenomegaly	Liver dysfunction
1	M	41	1,530	94	+	+	–	17,700	–	–	+	–	–
2	M	30	856	72	+	+	+	26,200	–	–	+	+	+
3	F	23	353	73	+	+	+	15,100	–	–	–	–	+
4	F	44	1,080	124	+	+	+	18,950	–	–	+	+	–
5	F	43	990	60	+	+	–	28,700	–	–	–	+	–
6	F	35	5,293	99	+	+	+	15,000	–	–	–	–	+

RF rheumatoid factor, *ANA* antinuclear antibodies

Table 2 Treatment and outcome

Case	Total disease duration (months)	Disease duration (in months) before treatment With CM	Previous inefficacious treatment	Efficacious treatment	ESR (mm at 1 h) changes (in months)	Outcome months to improvement	Months to stop treatment[a]
1	6	6	MTX 15 mg/week + MP 4 mg	CM 500 mg b.i.d. + MP 4 mg + MTX 15 mg/week	94→11 (3 months)	3 months ACR 70% MTX stopped for hepatic enzyme increase	12
2	60	12 (4th attack)	PDN 25 mg + MTX 15 mg/week + HCQ 200 mg + SSZ 2,000 mg	CM 500 mg b.i.d. + MP 8 mg +MTX 15 mg/week	40→7 (6 months)	6 months ACR 70% MTX stopped for nausea	18
3	3	3	–	CM 500 mg b.i.d. + MP 16 mg	73→15 (2 months)	2 months ACR 70%	6
4	6	6	i.v. MP + i.v. CP followed by MP 32 mg + MTX 15 mg/week	CM 500 mg b.i.d. + MP 16 mg +MTX 15 mg/week	40→13 (2 months)	2 months ACR 70%	7
5	3	3	PDN 12.5 mg + MTX 15 mg/week; MTX 15 mg/week + CsA 250 mg + MP 6 mg	CM 500 mg b.i.d. + MP 6 mg + MTX 15 mg/week	99→14 (3 months)	3 months ACR 50%	chronical treatment (CM 500 mg + MTX 10 mg/week + MP 6 mg)
6	200	1 (3rd attack)	–	CM 500 mg b.i.d. + MP 8 mg	99→10 (3 months)	3 months ACR 70%	9

PDN prednisone, *SSZ* sulphasalazine, *CS* cyclophosphamide, *CM* clarithromycin, *MP* methylprednisolone, *MTX* methotrexate, *CsA* cyclosporin A, *HCQ* hydroxychloroquine

[a] Months to improvement and months to stop treatment are measured from the start of the treatment with CM

In the Case 4 we also evaluated TNF-α and IL-6 levels which, in course of the previous ineffective treatment with high-dose GCs and MTX were as follows : TNF-α 28.6 pg/ml (normal values < 15.6 mg/ml) and IL-6 39.5 pg/ml (normal values < 12.5 pg/ml). Both TNF-α and IL-6 levels diminished to the normal level after 2 months of the treatment with CM.

In the Case 6 the disease onset was at the age of 16 and the patient had a second attack at the age of 18. With the treatment (indomethacin for 6 months) the patient had

achieved a complete remission lasting for 17 years without any further drug.

Discussion

The etiology of AOSD remains unknown. The design of a therapeutic scheme is complex since, at the present stage, the disease has no treatment guidelines. Consequently, most published papers include small cohorts of case-reports and only a few papers studied 6–20 patients. Here, we have described six cases of patients affected by AOSD that have been treated with CM added to low-mild dose of GC and MTX. In all six cases CM has confirmed to be efficacious in AOSD as in other inflammatory rheumatic diseases [12, 14, 16]. Indeed when CM was added to a mild-low dose of GC, five patients achieved a complete remission (ACR 70) and one patient achieved an incomplete remission (ACR 50%) at 6 months; five patients could stop any treatment in a mean time of 10 months, while the patient who did not reach the complete remission is currently chronically treated with CM, MTX and low-dose GC.

CM compared to biologic agents

In Table 3 our outcomes are compared with those obtained in other four papers where AOSD was treated with biologics agents. Our patients had a shorter disease duration, but higher ESR level and were treated from the beginning with a low dose of GC. The outcomes obtained with CM are very close to those obtained with anakinra [11] taking into account that in both studies most of the patients were treated with the drug as add-on therapy of MTX, while GC dosages were lower in our study.

Recent studies showed an important role of cytokines in the pathogenesis of the disease, but first experiences of treatment with anti-TNF-α blocking agents are not encouraging [4, 9, 10]. Fautrel in 2005 [4] reported about 20 cases of refractory AOSD treated with TNF-α blocking agents where the therapy was discontinued in 11 cases because of lack of efficacy, in 4 cases because of side effects, in further 2 cases for other reasons. If we consider four out of our six patients as refractory to DMARDs and high-dose GC, we can note that three of them obtained a complete remission (ACR 70%) and could stop completely the treatment, while only one (Case 5) obtained an incomplete remission (ACR 50%) and was obliged to continue the chronic treatment with CM added to MTX and low-dose GC. In that Case (no. 5) the treatment with CM was temporarily stopped because of severe metallic taste, the most common side effect of CM. However, after stopping CM, patient no. 5 had a relapse in 10 days. This fact shows once more that CM has a rapid onset of action and conversely a rapid lack of efficacy when stopped [14, 16]. Anyway, as CsA 250 mg daily added to MTX 17.5 mg/week and MP 10 mg daily did not give satisfying results (ACR < 20%), the patient was switched back to CM added to MTX 15 mg/week and low-dose GC obtaining an incomplete remission (ACR 50%).

Cytokines levels

We detected TNF-α and IL-6 levels only in Case 4, where they were elevated also in the course of the treatment with high-dose GC and MTX as well as in a previous treatment with i.v. high dose of GC added to i.v. CP. In this case CM was able to induce the remission in 2 months reducing the levels of anti-TNF-α and IL-6 to the normal values. This finding is in agreement with current reports about CM effectiveness in reducing cytokines independently from its antibiotic activity [18–20].

GC dose

Cases 2, 4 and 5 were previously treated with high-dose GC associated with either MTX or other DMARDs without reaching the remission. In Case 4 the (transient) previous remission was obtained only with intravenous high dose of MP (2 g) associated to intravenous CP. However the patient obtained a complete remission with CM added to a lower dose of GC in 2–6 months, and then the treatment could be stopped. In case 2, where high-dose GC added to MTX, HCQ and SSZ were ineffective, CM obtained the remission in 6 months adding MTX and low-dose GC. In Case 5 the treatment with CM was added to a low-dose GC to avoid worsening diabetes caused by previous, ineffective high dose of GC.

The Cases 1, 3 and 6 had never been treated with GC. Case 1 achieved complete remission in a short time using only 4 mg of MP added to CM. Since Cases 3 and 6 were two young women, they preferred to exclude MTX from the beginning; because of its teratogenicity, and use MP at low-mild dose added to CM instead. Complete remission was however achieved in only 2–3 months.

Mechanism of action

Ogrendik [15] hypothesizes that the oral anaerobic bacteria could be important in the etiopathogenesis of RA: he suspects that the efficacy of the drug could be related to its antibiotic activity against Gram-negative anaerobic bacteria considered as responsible for the periodontitis. However if RA is a bacterial disease, it would be difficult to justify the efficacy of MTX and other immunosuppressant drugs including GC in RA therapy [17]. On the other hand, Moskowitz [16] notices that the family of macrolide

Table 3 Comparison between treatment of AOSD with CM and biologic agents

Author	Number of patients, sex	Mean age	Disease duration (year)	Mean ESR before treatment (mm/1st h)	Previous ineffective treatments	Treatment	Associated DMARD	Mean GC dose	Outcome at 6 months
[10]	6 (2M 4F)	42.8	Not reported	53	MTX, CP, AZA, CsA	Infliximab 3–5 mg/kg	2 MTX, 1 AZA	5/6 > 10 mg PDN	6/6 partial remission
[9]	12 (2M 10F)	36.0	10.8	52	MTX	Etanercept 25 mg twice/week	MTX	11.3 mg PDN	2/12 withdrew (flare), 7/12 ACR 20%, 4/12 ACR 50%, 2 /12 ACR 70%
[4]	20 (25 treatments) (5M 15F)[a]	40.7	8.5	Not reported	MTX 20, iv Ig 5, HCQ 6, CsA 5, CP 4, AZA 3, others 6	Etanercept 25 mg × 2/week; or infliximab 3–5 mg/kg	12/20 MTX, 1/20 iv Ig, 1/20 AZA	25.6 mg PDN	4/20 non- responders, 5/20 complete remission, 11/20 partial remission
[11]	15 (4M 11F)	38.1	7.8	74	MTX 15, anti-TNF-α 10, iv Ig 5, others 8	Anakinra 100 mg/day	10/15 MTX, 2/15 Col, 1/15 MMF	26.8 mg PDN	11/15 ACR 50%, 9/15 ACR 70%, 8/15: GC reduction 45–75%
This study	6 (2M 4F)	36.0	3.9	75	MTX 4, CsA 1, HCQ 1, CP 1.	CM 500 mg b.i.d	4/6 MTX 15 mg/week	10.3 mg MP	5/6 ACR 70%, 6/6 ACR 50%, 5/6: GC reduction 50–100%

iv Ig intravenous polyvalent immunoglobulin, *Col* colchicine, *MMF* mycophenolate mofetil, *PDN* prednisone, *SSZ* sulphasalazine, *CS* cyclophosphamide, *CM* clarithromycin, *MP* methylprednisolone, *MTX* methotrexate, *CsA* cyclosporin A, *HCQ* hydroxychloroquine, *AZA* azathioprine

[a] Five patients switched etanercept and infliximab

antibiotics has non-antimicrobial effects. In particular the response of diffuse panbronchiolitis and other chronic respiratory infections to long-term macrolide therapy is an example of the anti-inflammatory and immunomodulatory activities of these drugs. In addition, CM is able to inhibit the production of IL-1β and TNFα in the lungs and is also able to inhibit cell mediator release and survival and to modulate IL-8 levels in chronic sinusitis and asthma [18, 19]. Moreover CM quickly inhibits TNFα production in a mouse model of septic shock, supporting the distinction between antimicrobial and anti-inflammatory properties of the drug [20].

Conclusions

Clarithromycin can be a useful drug to treat AOSD, because of its anti-inflammatory properties independent from its antibiotic activity. The association of CM with mild-low dose GC and MTX seems to be acceptable; thus permitting reduction of doses and administration of other drugs. Since CM gives a therapeutic advantage with no serious reported side effects and acceptable costs, it may represent a useful and valuable drug to be enclosed in a therapeutic algorithm for AOSD.

Conflicts of interest statement None.

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