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Efficacy and Safety of Intra-Articular Therapy with Methotrexate in Large Volume of Glucose Injection on Knee Synovitis in Patients with Ankylosing Spondylitis

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Abstract

Objective: To evaluate efficacy and safety of intra-articular therapy with methotrexate (MTX) in large volume of 10% glucose injection (GS) in ankylosing spondylitis (AS) patients with knee synovitis.

Methods: As patients with knee synovitis (n=90) were randomly divided into three groups. 50 patients in MTX/GS group were treated with intra-articular injection of MTX (15 mg)in 10% GS (20 ml) every week for 8 times, while 20 patients in GS group with intra-articular injection of 10% GS (20 ml) every week for 8 times, and 20 patients in control group without injection. All the patients received ibuprofen sustained release tablets 0.3 twice daily and Sulphasalazine 1 g twice daily. Same dose of MTX (15 mg once weekly) were given orally to the patients in GS group and control group. At the beginning of the treatment and after 4, 8 and 24 weeks, all the patients underwent a clinical evaluation, measuring maximum flexion-extension angle, knee pain with visual analog scale (VAS), swelling with joint circumference, global assessment (ASA20, PGA, BASMI,BASDAI, BASFI). Erythrocyte sedimentation rate (ESR) and C-reactive protein were tested.

Results: Joint pain, range of joint movement, circumference of swollen joint, ESR, CRP, patient's global assessment(PGA) in MTX/GS group are significantly improved after 4 weeks of treatment in comparison with baseline and other groups at same time point (P<0.01-0.05). Adverse reactions in MTX/GS group were less than other groups. No serious adverse events occurred in all the patients. Axial symptoms were no significant difference in three groups. At all-time point, MTX/GS group had better improvement in ASA20, BASMI, BASFI than other groups without statistic difference. No serious adverse events occurred in all the patients. Adverse reactions in MTX/GS group were less than other groups.

Conclusion: Compared to MTX orally taken, the repeated intra-articular injections of MTX glucose solution can suppress knee synovitis earlier and safely in AS patients. The intra-articular therapy of MTX/GS is another option in refractory monoarthritis.

Keywords: Ankylosing spondylitis; Intra-articular therapy; Knee synovitis; Methotrexate

Introduction

Some patients with inflamed arthritis can't respond effectively to routine anti-rheumatic therapy. Considering adverse effects and cost with aggressive systemic therapy, target intra–articular therapy in mono-oligoarthritis might be more effective and less harmful. Intra-articular injection can convey the drug directly to the inflamed joint area and avoid major systemic side effects. Since 2005, we have conducted intra-articular therapy with MTX (10-20 mg) in large volume (20-50 ml) glucose solution in some patients with refractory arthritis. Most of these patients responded well to the therapy. In order to provide clinicians with the highest level of evidence and evaluate the efficacy and safety of this intra-articular therapy, we conducted a 24-week trial in 90 ankylosing spondylitis (AS) patients with single knee synovitis since Nov. 2006.

Patients and Methods

Study design:

This study was carried out in accordance with the ethics principles. Informed consent was obtained from all patients. The study was designed as a randomized trial over 24 weeks in AS patients with single knee synovitis. Randomization was achieved through a computerized randomization/enrollment system. 90 enrolled patients were randomly assigned into three groups. 50 patients in MTX/GS group were treated with intra-articular injection of MTX (15 mg) in 10% Glucose solution (20 ml) every week for 8 times, while 20 patients in GS group with intra-articular injection of 10% Glucose solution (20 ml) every week for 8 times, and 20 patients in control group without injection. All the patients orally took ibuprofen sustained release tablets 0.3 twice daily and sulfasalazine 1 g twice daily for whole period. Same dose of MTX (15 mg once weekly) was given orally to the patients in GS group and control group. After 8 weeks of intra-articular therapy, three groups have same usage of MTX (15 mg/w) and sulfasalazine (1 g twice daily). All the patients underwent a clinical evaluation at baseline and 4th,

8th, 24th week of treatment, including measuring maximum flexion-extension angle, knee pain with visual analog scale (VAS), circumference of swollen joint, global assessment (ASA20, PGA, BASMI,BASDAI, BASFI). Erythrocyte sedimentation rate (ESR) and C-reactive protein were tested.

Patients

Enrolled patients with age from 16 to 56 years old were recruited from Nov. 2006 to Mar.2011inthe first affiliated hospital of Nanchang University. All patients met the modified New York criteria for AS [1] with active single knee synovitis. Active disease was defined according to 1) the composite Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score≥40 (mm on VAS) [2]. 2) Pain scores for knee joint ≥ 40 (mm on VAS), 3) elevated ESR or CRP. All patients had previously failed treatment with at least 1 NSAID and taken for at least 3 months at the maximum recommended or tolerated dose. Exclusion criteria included current or previous treatment with immuno suppressive or DMARD therapy within the 3 months prior to study entry. There is no significant difference in gender, age, each baseline index among three groups (Table 1).

	MTX/GS	GS	Control Group		P
N	50	20	20		
Gender (M/F)	37/13	15/5	14/6	X2=0.654	0.721
Age	29.96 ± 10.79	31.55 ± 8.69	31.95 ± 6.98	F=0.393	0.676
Knee pain scores mm on VAS	49.6 ± 14.3	47.5 ± 11.6	42.9 ± 19.9	F=1.392	0.254
PGA	4.89 ± 1.11	4.90 ± 0.79	4.85 ± 0.76	F=0.016	0.984
ESR(mm/h)	53.50 ± 30.22	50.15 ± 21.70	51.15 ± 20.58	F=0.134	0.875
CRP(mg/L)	32.04 ± 23.81	30.75 ± 19.53	29.30 ± 12.26	F=0.128	0.880
BASDAI mm on VAS	39.9 ± 10.4	43.7 ± 11.2	41.7 ± 19.1	F=0.629	0.535
BASFI mm on VAS	30.4±11.0	30.9±9.6	30.4±25.2	F=0.172	0.843
BASMI	3.20±1.31	3.00±1.49	3.05±1.67	F=0.008	0.992

Table1: Baseline demographic and disease characteristics of the patients in three groups.

Treatment

The patients in MTX/GS group were injected with MTX/GS solution (MTX 15 mg and 10% Glucose solution 20 ml) into knee joint after drawing off synovial fluid. Operations were same but injection was 10％Glucose solution (20 ml) for every patient in GS group. No injection for patients in Control group. All patients were injected once a week for 8 times. Ibuprofen sustained release tablets (0.3 twice daily) and sulfasalazine (1g twice daily) orally taken for whole period. Patients in GS group and Control group also take orally MTX 15 mg every week and same as patients in MTX/GS group after 8 weeks of intra-articular therapy.

Assessments

The primary efficacy endpoints were local improvement of knee joint and decreasing inflammatory factor of Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Assessing improvement of knee arthritis included maximum knee flexion-extension angle, knee pain scores on visual analog scale (VAS) and circumference of swollen joint. Improvement of swollen joint was defined as difference value of joint circumference between continuous two treatments. Reference value of ESR and CRP is less than 20 mm/h. and 8 mg/L, respectively.

Secondary efficacy end points included the proportion of responders according to the ASAS20 response criteria [3], patient's global assessment (PGA)[4], Bath AS disease activity index(BASDAI) [2], Bath AS functional index (BASFI)[5] and. Bath AS metrology index (BASMI) [6]. Complete blood count, urine test, liver and renal function test were conducted in all patients before treatment and at 4, 8,12,16,24 weeks of treatment.

Statistical analysis

All statistical analysis was performed using SPSS version 13.0 with nonparametric test, ANOVA and Spearman correlation coefficient. Descriptive variables are presented as mean value and standard deviation. Statistical significance was set at $P<0.05$.Mean values were calculated for all available time points.

Results

The primary efficacy endpoints (local improvement of knee joint and decreasing ESR and serum CRP level) (Figures 1 and 2).

After 4 weeks of treatment, maximum flexion-extension angle, pain scores of knee joint, circumference of swollen joint, ESR and CRP were significantly improved compared to baseline in MTX/GS group ($P<0.01$-0.05) while significant difference were found after 8 weeks of treatment between MTX/GS group with GS group and Control group ($P<0.01$-0.05). At week 8, mean value of CRP level and ESR were close to reference value in MTX/GS group. Improvements in maximum flexion-extension angle, circumference of swollen joint, ESR and CRP were significantly greater in the MTX/GS group than other groups ($P<0.01$-0.05). And the more improvement of knee pain scores in MTX/GS group than other groups was found at week 8 ($P=0.04$). The significant difference was sustained through week 24. Secondary efficacy end points (ASAS20, PGA, BASMI, BASDAI, BASFI)

At 4th week, 26% patients in MTX/GS group achieved ASAS20 response while 20% patients in the GS group and 15% in control group. At the 8th week and 24th week, the higher proportion of patients in MTX/GS group was sustained than other groups, but no significantly difference were seen among three groups (P=0.16, Figure 3).

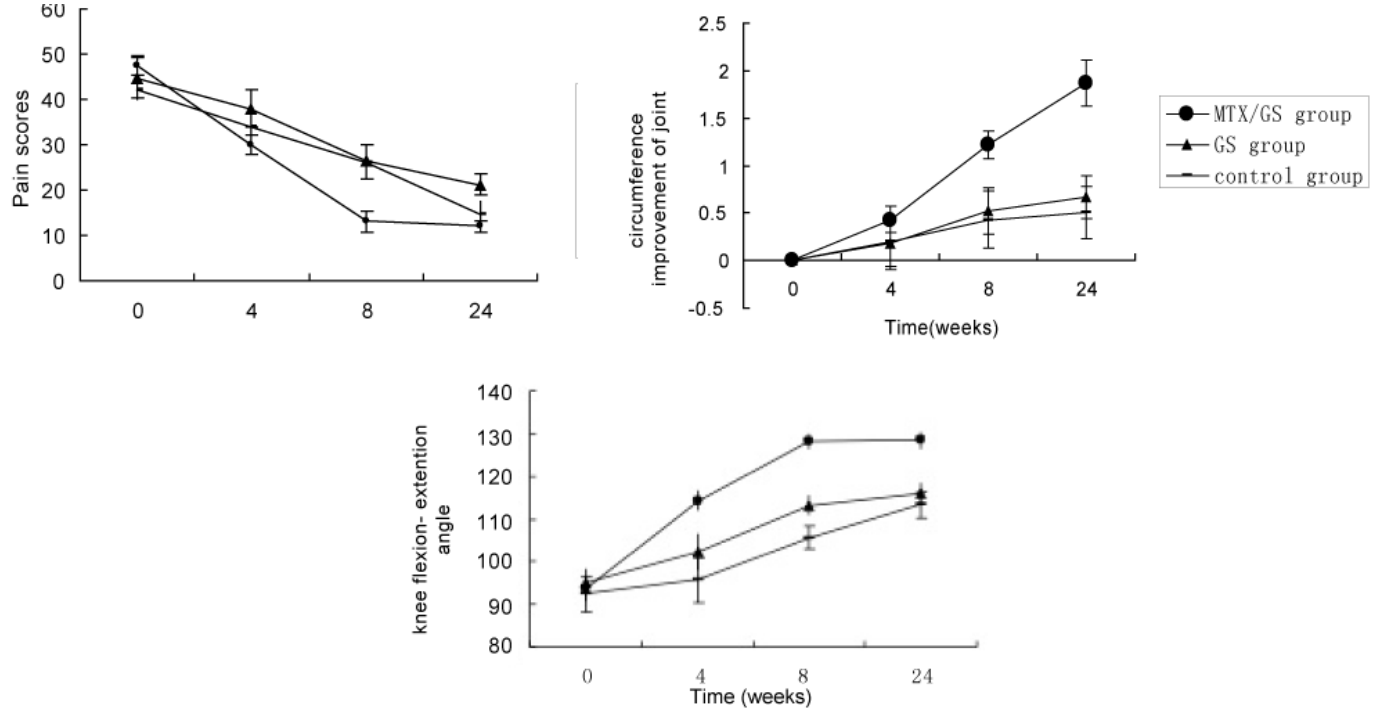

Figure 1: Improvement of knee joint after treatment. The numbers shown are the mean value from baseline to week 24 after treatment. Circumference improvement was defined as difference value of joint circumference in continuous twice treatments.

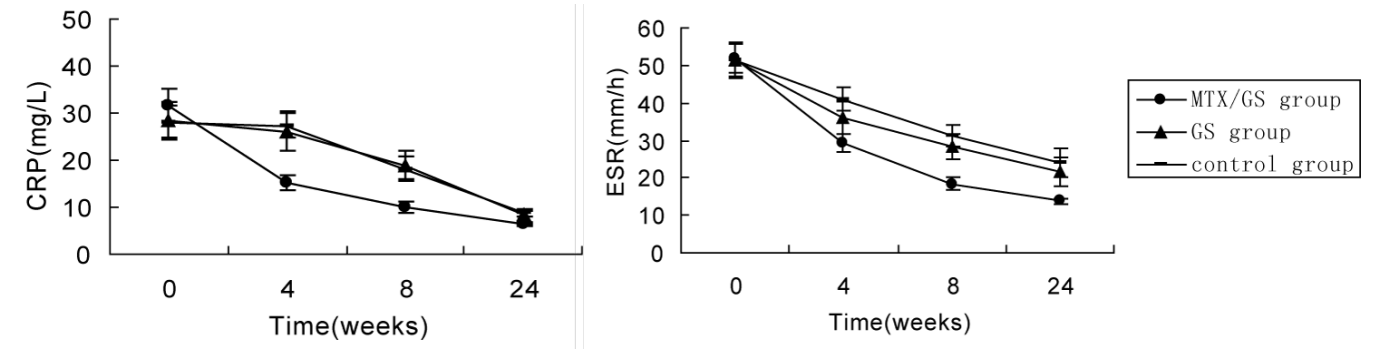

Figure 2: Serum CRP level and ESR in three groups from baseline to 24 weeks of treatment. The numbers shown are the mean value at week 0, 4, 8, 24 after treatment. At week 4, At week 4, CRP and ESR of the patients in MTX/GS group were significantly lower than other two groups(P<0.01-0.05). After 8 weeks of treatment, most patients in MTX/GS group reached reference value of ESR and CRP.

As an indicator of disease activity, BASDAI scores were decreased significantly as early as 4 weeks of treatment in MTX/GS group compare to other two groups which got significant difference from baseline at the 24th week (P=0.04). BASMI and BASFI in three groups were improved gradually from baseline at the 24th week without significant difference among three groups (P=0.47). PGA on mm VAS is assessed by patients themselves. The lower PGA scores suggest patients have higher satisfaction and better compliance. PGA scores were decreased gradually in three groups after treatment. Compare to baseline, significant improvement of PGA was found at the 4th week in the MTX/GS group (P<0.01) but at the 8th week in GS and control group (P<0.01). The significant difference was sustained to the end of trail (Figure 4).

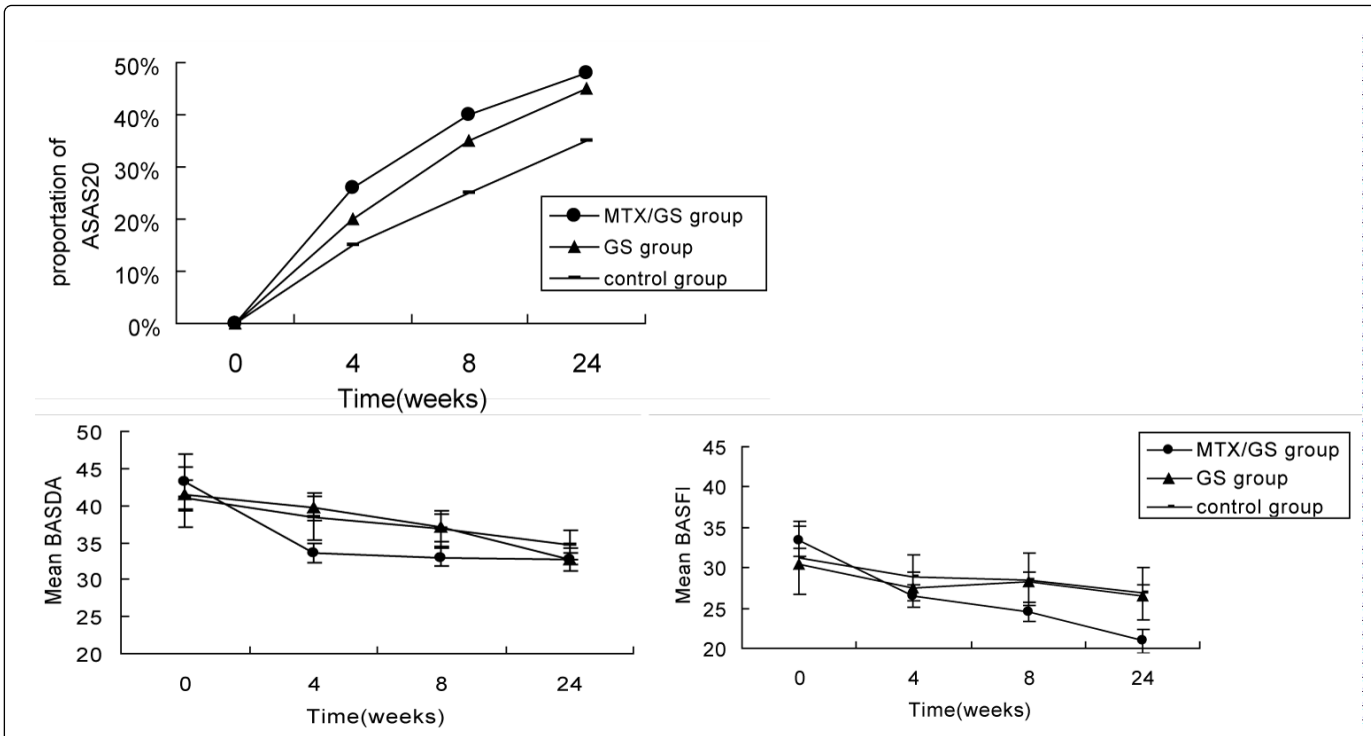

Figure 3: Proportion of the patients in three groups who achieved a treatment response for 24 weeks, according to the Assessment of Spondylo Arthritis international Society 20% improvement criteria (ASAS20). The numbers shown are the percentage of patients meeting the ASAS20 at each time point.

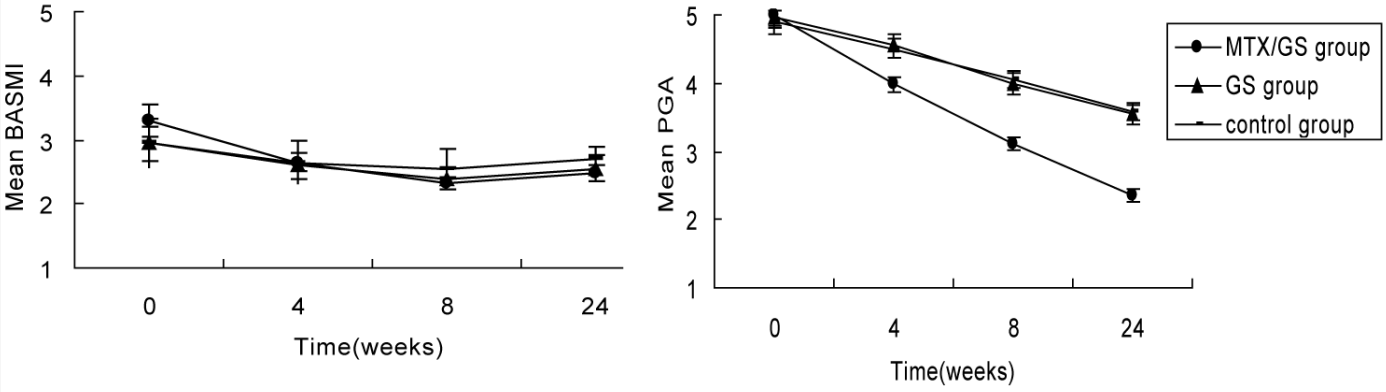

Figure 4: Mean scores on BASDAI, BASFI, BASMI and PGA from baseline to week 24 in three groups. The numbers shown are the mean scores at each time point. At week 4, BASDAI in MTX/GS group were significantly lower than other two groups ($P<0.05$).

Safety

The frequencies of adverse event are summarized in Table 2. No adverse event led to discontinuation and no serious adverse events occurred in three groups. No adverse events caused by intra-articular injection reactions. A significantly greater number of patients in the GS and control group than in the MTX/GS group reported experiencing gastrointestinal discomfort (25-30% versus 4%, respectively).

Discussion

Although ankylosing spondylitis (AS) is chronic inflammatory disease with major involvement of axial joints (especially the sacroiliac joints), peripheral arthritis also occurs in about a third of patients at disease onset. Reports in China showed 75% patients with AS have ever suffered from peripheral arthritis and it leads to the disability of 36% young patients with AS [7]. To prevent irreversible damage and protect joint function, it is important to control synovitis as early as

possible. Our study shows intra-articular MTX/GS injection can effect earlier than MTX orally taken in AS patients with knee synovitis. Knee pain, range of joint movement, joint swelling, ESR, CRP and PGA in MTX/GS group were significantly improved at the 4th week of treatment in comparison with baseline and other groups at same time point (P<0.01-0.05). At all other time points, MTX/GS group had better improvement in global assessment of ASA20, BASMI, BASFI than other groups. Adverse reactions in MTX/GS group were less than other groups. No serious adverse events occurred in all the patients. The 24-week results of this study provide strong evidence that intra-articular injection of MTX in large volume glucose solution is effective and safe therapy on mono-arthritis in AS patients.

Groups	N	Decreased White blood cell	Liver function disorder	Abnormal urine test	Gastrointestinal Discomfort	Total
MTX/GS group	50	1 （2%）	2 （4%）	1 （2%）	2 （4%）	5 （10%）
GS group	20	1 （5%）	2 （10%）	0	5 （25%）	6 （30%）
Control Group	20	0	3 （15%）	1 （5%）	6 （30%）	6 （30%）

Table 2: Safety findings in three groups through week 24*.*Values are the number (%) of patients.

Intra-articular therapy has a long history in treating inflamed arthritis, especially mono-oligoarthritis. Many different compounds are used. The most common injection is corticosteroids that can relieve rapidly and effectively joint pain and swelling. But the efficacy is transient and frequent administration do harm to cartilage [8]. Unsatisfactory results also were shown on other intra-articular injections such as NSAIDs and traditional Chinese medicine. Since 1970's, a number of short-term studies have demonstrated intra-articular administration of MTX can inhibit toxic oxygen metabolite release, lymphocyte proliferation and production of tumor necrosis factor alpha (TNF-a), interleukin (IL)-6 and IL-8 on the synovial membrane [9]. The therapy of MTX i.e. was gradually used in juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA), psoriasis arthritis (PsA) and knee synovitis with possibly favorable results and rare negative side effects. But MTX has a short-time sustained effect in joint because of a rapid clearance from joint cavity. In order to maintain effectiveness of MTX in joint cavity, researchers have studied on new form of MTX to prolong the residence time of the drug in the joint cavity, such as liposomal conjugated MTX which can produce a rapid and sustained effect in the joint cavity [10].

In the MTX/GS injection, we use a large volume of 10% glucose solution (GS) to release adhesive tissue by fluid tension, which already was shown benefit to joint function recovering and life quality increasing [11]. It is found the patients with arthritis have lower level of glucose and protein in synovial fluid which was considered as an important factor aggravating inflammation and damage of joint [12]. As a kind of hypertonic solution, it can increase osmotic pressure in joint cavity and relieve tissue edema. A large volume of 10% GS also can provide nutrition and dilute inflammatory factors in joint cavity. So combining with large volume of 10% GS can enhance anti-inflammation of intra-articular injection of MTX, meanwhile, improve metabolism environment in joint cavity.

Two key points should be emphasized in the MTX/GS therapy. One is the volume of GS should be enough which depend on different joints, usually about 40 ml for hip and 20 ml for knee. Another important point is pushing the solution out of syringe rapidly when syringe needle is punctured into joint cavity and meanwhile kneading around joint. The solution serves as a 'liquid scalpel' to separate adhesive tissue and release tissue edema without any injury compare to real scalpel.

In conclusion, our study demonstrated intra-articular MTX/GS injection has advantage of suppressing inflamed joints rapidly and effectively. We suggest it is therapeutic choice not only for AS patients with mono-oligo-arthritis but also for other rheumatic disease with refractory mono-arthritis. Further study should be conducted to investigate the best dose and course of the intra-articular therapy with MTX and GS. Also we anticipate appropriate intra- articular form of MTX come into market.

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References

1. van der Linden S, Valkenburg HA, Cats A (1984) Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 27: 361-368.
2. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, et al. (1994) A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 21: 2286-2291.
3. van der Heijde D, Dougados M, Davis J, Weisman MH, Maksymowych W, et al. (2005) Assessments in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. Arthritis Rheum 52:386-94.
4. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M (2001) Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 44: 1876-1886.
5. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, et al. (1994) A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 21: 2281-2285.
6. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, et al. (1994) Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 21: 1694-1698.
7. Wu Donghai, Wang guochun. (2008) Clinical Rheumatology, first version. Beijing: People health press.
8. Wei AS, Callaci JJ, Juknelis D, Marra G, Tonino P, et al. (2006) The effect of corticosteroid on collagen expression in injured rotator cuff tendon. J Bone Joint Surg Am 88: 1331-1338.
9. Iagnocco A, Cerioni A, Coari G, Ossandon A, Masciangelo R, et al. (2006) Intra-articular methotrexate in the treatment of rheumatoid arthritis and psoriatic arthritis: a clinical and sonographic study. Clin Rheumatol 25: 159-163.
10. Williams AS, Camilleri JP, Goodfellow RM, Williams BD (1996) A single intra-articular injection of liposomally conjugated methotrexate suppresses joint inflammation in rat antigen-induced arthritis. Br J Rheumatol 35: 719-724.
11. Zeng Xingruo, Huang Anbin, Wang Feng. (2007) Observe the clinica l effect on ankylosing spondylitis by hip joint fluid relax operation. Chinese journal of practical internal med icinem : 458-460.

12. Arrich J, Piribauer F, Mad P, Schmid D, Klaushofer K, et al. (2005) Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. CMAJ 172: 1039-1043.