Excellent Endpoints from Step-Down Bridge Combination Therapy of 5 Immunosuppressants in NSAID-Refractory Ankylosing Spondylitis: 6 Year International Study in Asia — WHO-ILAR COPCORD Stage II Treatment of the Autoimmune Diseases

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ABSTRACT. ***Objective***. To achieve induction and maintenance of remission in ankylosing spondylitis (AS) refractory to nonsteroidal antiinflammatory drugs with "step-down bridge combination" of 5 immunosuppressants, as an alternative to costly biologic DMARD. Primary endpoints were the percentage of patients achieving ASAS 20 at the end of Year 6; secondary endpoints were patients achieving ASAS 50 and ASAS 70, induction and maintenance of clinical and radiological remission, and the side effects of this combination of immunosuppressive drugs.

Methods. In a 6-year uncontrolled international open-label prospective study, 54 men and 25 women with AS were enrolled after exclusion criteria were applied. Included patients were treated with individualized combinations of low-dose intravenous methylprednisolone + cyclophosphamide + methotrexate (for the first 6 mo). When erythrocyte sedimentation rate dropped to ≤ 20 mm (men ≤ 10 mm), low-dose oral mycophenolate mofetil and cyclosporine were prescribed for at least 2 years. Assessments were executed at baseline, Weeks 1 and 2; Months 1, 2, 4, and 6; and Years 1, 2, 4, and 6.

Results. After 15/79 dropouts were accounted for, 64/79 patients achieved ASAS 20, ASAS 50, and ASAS 70. Disease remission occurred in 60/79 at 6 months when IV drugs were tapered. Gastrointestinal side effects were observed in 20/79 patients; no liver, renal, cardiovascular, and hematologic adverse effects were observed.

Conclusion. Step-down bridge combination of 5 immunosuppressants achieved ASAS 20, ASAS 50, and ASAS 70 in 64/79 patients, and remission in 60/79 patients with NSAID-refractory AS. Controlled studies are needed to confirm this method, and to study the role of these different drugs in developing countries in Asia, where the majority of patients with NSAID-refractory AS are unable to obtain treatment with tumor necrosis factor-α blockers. (J Rheumatol 2006;33:2484–92)

Key Indexing Terms:
NSAID-REFRACTORY ANKYLOSING SPONDYLITIS IMMUNOSUPPRESSIVE AGENTS ASSESSMENT IN ANKYLOSING SPONDYLITIS RESPONSE CRITERIA REMISSION

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Ankylosing spondylitis (AS) is an autoimmune disease characterized by chronic progressive inflammatory arthritis affecting mainly the axial and to a lesser extent the peripheral joints; and by axial and peripheral enthesitis.

Cyclooxygenase 1 (COX-1) or COX-2 nonsteroidal antiinflammatory drugs (NSAID)[1] and physical therapy have been the standard treatment for AS[2]. Sulfasalazine shows variable benefit in peripheral joints in the short term[3]. NSAID neither stop nor slow the progression of AS; rather, their use is associated with notorious liver[4], gastrointestinal[5] (GI), and renal[6] toxicity, with a high dropout rate. A substantial proportion of patients have NSAID-refractory AS (NR-AS) (Appendix). In some patients NSAID, sulfasalazine, and corticosteroids do not satisfactorily control AS[7].

Several uncontrolled studies have evaluated agents as monotherapies in AS, including methotrexate (MTX)[8,9], pulse intravenous (IV) methylprednisolone (MPS)[10] and cyclophos-

phamide (CYC)[11], oral cyclosporine[12], and mycophenolate mofetil (MMF)[13], and results have shown varying efficacy. A single immunosuppressant (IMN) does not suppress all mediators of autoimmune inflammation, as reflected in the various types of cytokines and autoantibodies of the inflammatory process. Cytokine gene expression comparable to that of rheumatoid arthritis[14] makes AS responsive to similar therapy. Therefore, combination therapy may be required when treating NR-AS with MTX[8,15]. An alternative therapy is required after standard treatment fails.

The natural history of AS shows continuous linear progression of radiological changes; over a period of 10 years disease progresses about 35% radiologically. Radiological cervical spine progression is a function of disease duration, severity of lumbar and hip involvement, and history of iritis[16].

We based our initiative on the above considerations and on principles of the Community Oriented Program for Control Of Rheumatic Disease (COPCORD) to achieve less expensive research on epidemiology. COPCORD is a World Health Organization-International League of Associations for Rheumatology program comprising 3 stages: (1) Epidemiology, (2) Intervention by Education and Treatment, and (3) Identification of Environmental and Genetic Risk Factors of the Rheumatic Diseases[17]. Following trial and error after more than 5 years since 1994, JD has formulated step-down bridge combination therapy of 5 immunosuppressants (SBC-5-IMN) for autoimmune disease[18] including NR-AS.

In the context of the high cost of biologic disease modifying antirheumatic drugs (DMARD), we conducted a 6-year, uncontrolled open-label prospective international study in Asia of induction and maintenance of remission in NR-AS with SBC-5-IMN.

MATERIALS AND METHODS

Fifty-four male and 25 female Han Chinese Indonesians with active AS, as defined in the Appendix, who were refractory to NSAID and treated with physical therapy from January 1996 to January 1999, were entered in the study after exclusion criteria had been applied (Table 1). The coordinating investigator (JD) and coauthors evaluated all patients at all visits at their own centers.

The primary endpoint was the ASsessments in Ankylosing Spondylitis Working Group 20 (ASAS 20) criteria[19]; secondary endpoints were ASAS 50, ASAS 70, remission with or without drug (Appendix), radiological normalization, and radiological remission (Appendix). Other response criteria such as ASAS 40 and 5 of the 6 criteria were also assessed[20].

To determine efficacy and adverse effects of therapy, besides standard baseline laboratory procedures, we monitored clinical evaluations of ASAS 20, 50, and 70 responders; Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[21]; Functional Index (BASFI)[22]; Global Score (BAS-G)[23]; and Mobility Index (BASMI)[24] at baseline, and at 1, 2, 4, 8, 16, 24, 48, 96, 192, and 288 weeks (Table 2). Erythrocyte sedimentation rate (ESR)[25] and C-reactive protein (CRP)[26] were assessed weekly from baseline until start of fortnightly intravenous therapy (IVT) sessions. Additionally, ESR was recorded whenever required.

Bath Ankylosing Spondylitis Radiology Index for the spine[27] (BASRI-s) and for the hip[28] (BASRI-h) were scored at baseline and biannually to measure radiological progression or response to therapy. Radiographs were read unblinded by JD and blinded by ARN. Minor differences in BASRI readings were discussed until agreement was reached. After 6 years dropouts for whom data were available (Appendix) were scored with BAS clinical and radiological indexes, CRP, ESR, ASAS 20, ASAS 50, and ASAS 70.

Medications. The schedules of SBC-5-IMN are: intensive IVT with 3 IMN to achieve remission before irreversible organ damage has occurred; when ESR declines to < 20 mm (male < 10 mm) step-down oral maintenance therapy with 2 IMN are prescribed; when remission (Appendix) is achieved IVT is tapered; after 2 years in remission with oral drugs (RworalD), oral drugs are tapered to remission without drug (RwD) or remains longterm in RworalD.

Rationale for combination therapy. Combining low dosages of IMN enhances efficacy due to common receptor sites. Dose-dependent hematogenic adverse effects are minimized or prevented because of the different receptor sites and the low dosages of IMN. GI symptoms that are induced by IMN at common receptor sites can be minimized or prevented by preceding IVT with a general anti-emetic, antispasmolytic, or proton pump inhibitor. All oral drugs such as NSAID, corticosteroids, azathioprine, sulfasalazine, MTX, hydroxychloroquine, or chloroquine phosphate at presentation were stopped. After 2 week washout, the first IVT session of SBC-5-IMN concomitant with empirical weekly polyarticular (PA) injections of corticosteroids and needling of trigger points of enthesitis and secondary fibromyalgia were initiated.

Patients with no history of GI symptoms commence with the maximum dosage of 100 mg CYC + MPS/IV 5-fluorouracil (5FU) and 12.5 mg of MTX, or based on 1.5 mg/kg/body weight (kg/bw) of IV dosage of CYC + MPS/IV 5FU per daily (5 times weekly) session and 0.2 mg/kg/body weight MTX once weekly. Those who have a history of GI symptoms start a minimum dosage of 25 mg CYC + MPS/5FU and 5 mg MTX. When reduction of ESR is < 1 mm per week, dosage is raised by increments of 25 mg CYC + MPS/5FU and 2.5 mg MTX to 50, 75, and 100 mg of CYC + MPS/5FU and 7.5, 10, and 12.5 mg of MTX. For ease of administration 25, 50, 75, and 100 mg of CYC + MPS/5FU and 5, 7.5, 10, and 12.5 mg of MTX are the fixed standard dosages. To minimize GI symptoms a wide range of dosages are applied.

When GI symptoms persist, one or more of the following are started and then given preventively prior to each treatment: IV anti-emetic, antispasmolytic, proton pump inhibitor, and granisetron. When maximum dosages are reached and ESR has not dropped to < 1 mm per week compared with 2 previous weekly measurements, the patient is considered refractory to SBC-5-IMN. Consequently, these measurements require weekly monitoring of ESR from initiation of IVT session to tapering of IVT session when remission is achieved.

When ESR decreases to ≤ 20 mm (men ≤ 10 mm), non-intensive low-dose oral maintenance therapy of MMF 500 mg and/or cyclosporine 50 mg 2 or 3 times daily is prescribed, while IVT daily sessions 5 times per week continue until remission is obtained. When ESR is suppressed to ≤ 10 mm (men ≤ 5 mm), the IVT sessions are tapered as follows: 3×, 2×, 1× weekly; 1× fortnightly; 1× monthly; and terminated at 1× 2-monthly (9 IVT sessions are tapered over a period of 17 wks); and RworalD are started. With every doubling of the interval between IVT sessions, the ESR is checked. When ESR remains stationary or increases to > 1 mm, the frequency of IV sessions is increased to the previous level. When ESR continues to decline > 1 mm, the intervening period is doubled. When the IV session is given once fortnightly, the IV MTX can be switched to an equivalent oral weekly dose if required.

Empirically, IV 5FU 25–100 mg replaces the IV MPS when: diabetes mellitus is present or corticosteroid-induced hyperglycemia occurs, history of melena and/or hematemesis is reported, or IV corticosteroid-induced gastric intolerance occurs. In aged patients (> 65 yrs), physiological functions and anatomical resilience decline > 25%, and the NR-AS is less active and progresses slowly. Low and middle ranges of the recommended dosages suit the aged patients, with minimum dose-dependent adverse effects while retaining efficacy due to the combination.

Concomitant with initiation of IVT, weekly PA injections with corticosteroid 0.025–0.500 cc are carried out. PA injections and needling with corticosteroid 0.025 to 0.500 cc, using 1 cc syringe with varying needle sizes from

Table 1. Demographic data, disease duration, and status of the 79 patients with NSAID-refractory AS at presentation and final evaluation in number.

Group	BASRI < 2, N = 54	BASRI > 2, N = 25	Total, N = 79
Men	39	15	54
Women	15	10	25
Age at disease onset, yrs, range	12–56	11–59	11–59
Age at disease onset, yrs, mean	27.2 ± 13.3	25.7 ± 13.6	26.8 ± 13.9
Disease duration, yrs, range	4.4 ± 1.4–12.5 ± 3.7	4.5 ± 1.3–20.4 ± 7.1	4.4 ± 1.3–20.4 ± 7.1
Disease duration, mean ± SD, yrs	8.1 ± 1.3	12.5 ± 4.2	9.5 ± 2.5
Final evaluation, n	675		
Dropouts	10/54	5/25	15/79
Men	6/39	3/15	9/54
Women	4/15	2/10	6/25
ASAS 20	1/10	0	1/15
Cases completing treatment	44/54	20/25	64/79
Men	33/39	12/15	45/54
Women	11/15	8/10	19/25
ASAS 20, ASAS 50, and ASAS 70	44/54	20/25	64/79
Remission with oral drugs	—	16/25	16/79
Remission without drugs	44/54	—	44/79
Not in remission	—	4/25	4/79

ASAS: Assessments in Ankylosing Spondylitis Working Group. BASRI: Bath AS Radiology Index.

Table 2. Results of periodic evaluations of the laboratory, clinical, functional, and radiological variables in achieving remission with oral drugs and remission without drug of 79 patients with NSAID-refractory AS after 15 subjects dropped out.

	Baseline	1 week	2 weeks	4 weeks	8 weeks	16 weeks	24 weeks	48 weeks	96 weeks	192 weeks	288 weeks
BASRI < 2, N = 44											
ESR F	84.2 ± 36.8	47.4 ± 14.3	33.4 ± 10.8	24.3 ± 5.7	16.7 ± 5.1	15.3 ± 4.2	14.4 ± 4.2	13.4 ± 3.1	12.5 ± 3.2	12.3 ± 3.1	12.3 ± 3.2
ESR M	85.7 ± 31.5	45.8 ± 18.3	25.9 ± 12.3	17.2 ± 9.1	7.4 ± 2.3	6.3 ± 2.1	6.4 ± 2.4	6.1 ± 1.8	5.9 ± 1.8	5.2 ± 1.6	5.0 ± 1.5
CRP	135.1 ± 38.2	71.1 ± 20.2	34.6 ± 12.5	16.8 ± 4.2	2.1 ± 0.8	2.1 ± 0.7	2.0 ± 0.6	2.0 ± 0.5	1.8 ± 0.3	1.5 ± 0.3	1.3 ± 0.3
BASDAI	6.19 ± 2.07	4.9 ± 1.1	3.7 ± 0.9	2.4 ± 0.4	1.2 ± 0.3	0.6 ± 0.3	0.6 ± 0.2	0.6 ± 0.2	0.5 ± 0.3	0.4 ± 0.2	0.3 ± 0.1
BASFI	5.55 ± 1.91	3.2 ± 1.2	2.3 ± 0.9	1.9 ± 0.8	1.4 ± 0.5	1.3 ± 0.4	0.8 ± 0.1	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.5 ± 0.1
BAS-G	6.9 ± 1.7	3.4 ± 1.1	1.7 ± 0.4	1.1 ± 0.3	0.7 ± 0.2	0.6 ± 0.2	0.5 ± 0.3	0.4 ± 0.3	0.3 ± 0.2	0.2 ± 0.1	0.2 ± 0.1
BASMI	7.31 ± 2.5	3.3 ± 1.4	1.6 ± 0.4	1.1 ± 0.3	0.7 ± 0.2	0.5 ± 0.3	0.5 ± 0.3	0.4 ± 0.3	0.4 ± 0.2	0.3 ± 0.1	0.2 ± 0.1
BASRI-s	1.5 ± 1.3	—	—	—	—	—	—	—	0.3 ± 0.1	0.2 ± 0.1	0.1 ± 0.1
BASRI-h	1.6 ± 0.3	—	—	—	—	—	—	—	0.3 ± 0.1	0.2 ± 0.1	0.1 ± 0.1
BASRI ≥ 2, N = 20											
ESR F	105.4 ± 35.7	61.2 ± 23.7	39.1 ± 11.6	26.3 ± 5.9	20.2 ± 4.2	15.4 ± 4.5	15.3 ± 4.4	14.4 ± 4.1	13.5 ± 3.2	13.1 ± 3.1	12 ± 3.0
ESR M	107.3 ± 33.9	43.4 ± 14.5	23.1 ± 9.1	12.4 ± 3.7	7.5 ± 2.1	6.3 ± 3.1	6.1 ± 3.2	6.0 ± 2.6	5.9 ± 3.1	5.8 ± 2.6	5.7 ± 2.4
CRP	223.8 ± 66.9	142.9 ± 44.4	49.8 ± 16.8	12.8 ± 5.1	2.3 ± 0.6	2.2 ± 0.6	2.3 ± 0.5	2.2 ± 0.4	2.2 ± 4	1.9 ± 0.3	1.8 ± 0.3
BASDAI	7.96 ± 1.53	5.15 ± 2.11	3.35 ± 1.32	1.82 ± 0.52	0.77 ± 0.21	0.71 ± 0.22	0.70 ± 0.24	0.69 ± 0.21	0.63 ± 0.3	0.59 ± 0.23	0.50 ± 0.1
BASFI	7.91 ± 1.49	4.32 ± 1.62	3.83 ± 0.94	2.97 ± 0.71	1.76 ± 0.33	1.55 ± 0.34	0.75 ± 22	0.74 ± 0.22	0.71 ± 0.17	0.71 ± 0.14	0.51 ± 0.23
BAS-G	7.3 ± 2.2	5.9 ± 3.4	3.6 ± 0.2	1.9 ± 0.3	0.7 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.5 ± 0.1	0.4 ± 0.1
BASMI	7.07 ± 2.81	4.11 ± 1.77	2.56 ± 0.65	1.33 ± 0.31	0.67 ± 0.31	0.65 ± 0.31	0.63 ± 0.32	0.61 ± 0.31	0.58 ± 0.28	0.57 ± 0.21	0.51 ± 0.15
BASRI-s	2.8 ± 0.9	—	—	—	—	—	—	—	2.8 ± 0.8	2.8 ± 0.8	2.8 ± 0.17
BASRI-h	2.1 ± 0.9	—	—	—	—	—	—	—	2.1 ± 0.6	2.1 ± 0.6	2.1 ± 0.5

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Bath Ankylosing Spondylitis Indexes: BASDAI: Disease Activity, BASFI: Functional, BAS-G: Global, BASMI: Metrology, BASRI-s: Radiology-spine, BASRI-h: Radiology-hip.

22 G × 1.5 in to 26 G × 0.5 in, were performed into various joints, from distal interphalangeal to sacroiliac and hip joints (needle size 25 G × 3.5 in). Corticosteroid 0.025 cc with a distance of 5 mm between needle points of entry was infiltrated into areas (around trigger points) of painful enthesitis and fibromyalgia. Corticosteroid 1 cc comprises 0.6 cc triamcinolone acetonide (TA, from a 5 cc vial of 40 mg TA) + 0.2 cc dexamethasone (DxM, from 1 cc ampoule of 5 mg DxM) + 0.2 cc lignocain (LNC, from a 2 cc ampoule of 2% LNC). Thus 1 cc of corticosteroid mixture contains 4.8 mg TA, 1 mg DxM, and 4 mg LNC. Our rationale for the mixture: instant anesthesia up to 4 h by LNC; efficacy of DxM commences after 4 h and for up to 4 days; efficacy of TA is effective after 4 days up to < 6 days. Efficacy of PA injection lasts at least 10 days. When local visual analog scale (VAS) pain is < 1 (scale 1–10), weekly PA injections are terminated. Analgesics including paracetamol and tramadol HCl were permitted when required. All patients were required to report by cell phone or telephone during office hours when adverse effects or fever occurred.

After 2 year consolidation of RworalD, attempts are made to taper oral therapy over a period of 1 year without flare (Appendix) to RwD. Oral MTX is first tapered from once weekly to fortnightly over an arbitrary period of 12 weeks and stopped. MMF is then tapered from 500 mg 3 times weekly in decreasing daily frequency over a variable period of 8–12 weeks depending on flare and stopped. Finally, CyS is tapered in similar fashion. If 2 flares occur within 1 year during tapering, oral drugs are continued longterm with no further attempts to taper.

Flare (Appendix) during RworalD and RwD must be immediately suppressed by reinstitution of daily 5× weekly IVT and weekly PA injection. Combination IV MPS/5FU + CYC + MTX is adequate to reinduce remission during flare. The relatively low dosages, as adapted to the individual, of oral combination of MMF + CyS and/or MTX cannot induce remission or suppress flare. Higher oral dosages resulting in gastric intolerance are required for induction of remission or suppression of flare.

Statistics. Analyses were performed using the SPSS software, version 11.5. Per-protocol analysis was carried out for dropouts. Chi-square analysis was performed for significance of the distribution of clinical and laboratory variables.

RESULTS

Of the 91 eligible patients, 12 were excluded for various reasons, 79 were treated, but only 64 were analyzed due to 15 dropouts (Figure 1).

All sacroiliac joints were injected each with 0.5 cc corticosteroid mixture. The total number of axial (including cervical facet joints) and peripheral joints injected per session in patients with BASRI score < 2 was mean 2.5 ± 0.5 joints, and in patients with BASRI score ≥ 2 it was mean 4.3 ± 0.9 joints. The total number of weekly PA injections in patients with BASRI score < 2 was mean 4.3 ± 1.1 and in patients with BASRI ≥ 2 it was mean 5.2 ± 1.9 times. Quantity of corticosteroid mixture injected weekly in patients with BASRI score < 2 was mean 1.9 ± 0.4 cc and with BASRI score ≥ 2 it was mean 2.8 ± 0.8 cc per PA session. Corticosteroid needling into and around trigger points of enthesitis and fibromyalgia was executed at the same frequency as PA injections. The total cumulative dosage of CYC, MPS, MTX, and PA corticosteroids in patients with BASRI score < 2 was mean 1281.2 ± 413.7 mg, 748.3 ± 151.3 mg, 105.8 ± 27.9 (Table 3), and 9.0 mg TA ± 1.9 mg DxM; and in patients with BASRI score ≥ 2 it was mean 1942.7 ± 401.8 mg, 1304.8 ± 278.1 mg, 152.3 ± 33.2 (Table 3), and 13.4 mg TA ± 2.8 mg DxM, respectively.

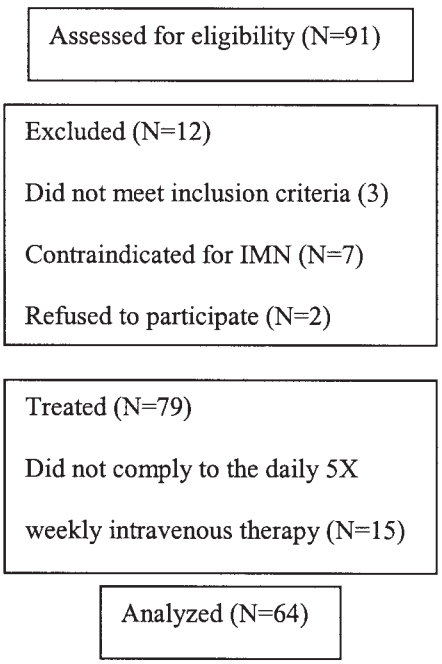

Figure 1. Progress of 91 eligible patients with NSAID refractory AS over 6 years.

Weekly reduction of ESR was mean 2.9 ± 1.2 mm with a range of 1.0–7.2 mm by IVT during the first 6 months. Number of cases achieving ESR < 10 mm at 3 weeks was 1, 4 weeks 2, 5 weeks 4, 6 weeks 7, 7 weeks 10, 8 weeks 11, 9 weeks 12, and at 10 weeks 13 cases (Figure 2).

Mean titer of CRP was normalized (≤ 3 mg %) in mean 8 weeks (Table 2), and ESR in mean 10 weeks, except where there was chronic infection (mostly dental structures, see Figure 1). Almost all female and male patients achieved ESR of mean < 20 mm in 4 months. The BASDAI, BASFI, BASMI, and BAS-G scores were mean < 1 (scale 0–10) in 6 months (Table 2). In less than 6 months almost all patients fulfilled criteria to start oral therapy when the last IVT session was terminated. ASAS 20, ASAS 50, and ASAS 70 were achieved in 64/79 of the cases. Clinical remission occurred in 60/79 cases comprising 44/54 patients in the group with BASRI score < 2, and 16/25 patients in the group with BASRI score ≥ 2 (Table 1). In almost all patients, moderate to severe pain was reduced at 4 months with VAS pain score and BASDAI < 1, but not BASFI (Table 2). This improvement was associated with ESR ≤ 20 mm and CRP ≤ 3 mg % or negative (Table 2). ASAS 20 of the 15 dropouts for whom data were available in the group with BASRI score < 2 was noted in 1/15 cases (Table 1). The early dropouts were due to noncompliance to the fixed and complex treatment schedules.

In the patients with BASRI score < 2 the secondary endpoints were radiological normalization (Appendix) of the axial and/or peripheral joints, with BASRI scores ranging from < 2 to 0, inclusive of RwD, in 44/79 patients. In the patients with BASRI score ≥ 2 the secondary endpoints of ASAS 50 and ASAS 70 were achieved in 20/79 cases. Radiological remission and RworalD occurred in 16/79 patients. The RwD was not achieved in those in the group with BASRI score ≥ 2 (Table 1) and in those who were IMN nonnaive NR-AS, but ASAS 70 was obtained. Only those with BASRI score < 2 and who were IMN-naive NR-AS patients achieved RwD.

Flare occurred after mean 2.1 ± 0.5 years in 15/16 patients who were in RworalD. Flare rate per patient-year in the RworalD group was 0.156. Flare occurred in 11/44 patients after mean 3.7 ± 1.3 years in RwD. Flare rate per patient-year in RwD was 0.042.

The median duration of RworalD was 4.8 years and RwD was 2.9 years, excluding the relatively short period of flare of

Table 3. The mean daily, weekly, and total cumulative IV dosages in mg, total number of intravenous therapy (IVT) sessions, and duration of IV of cyclophosphamide, methylprednisolone, and methotrexate in the treatment of NSAID-refractory AS.

	Cyclophosphamide, mg, range 25.0–100.0		Methylprednisolone, mg, range 25.0–100.0		Methotrexate per week, mg, range 5.0–12.5	
Radiologic Grade	BASRI < 2	BASRI ≥ 2	BASRI < 2	BASRI ≥ 2	BASRI < 2	BASRI ≥ 2
Daily IV dosage, mg, 5 × per week	35.1 ± 8.5	45.7 + 14.9	20.5 ± 7.9	30.7 ± 9.6	—	—
Weekly cumulative dose, mg	175.5 ± 32.9	228.5 ± 39.7	122.5 ± 29.7	153.5 ± 36.3	7.2 ± 2.7	9.7 ± 2.7
Total IVT sessions	36.5 ± 9.1	42.5 ± 10.9	36.5 ± 9.1	42.5 ± 10.9	14.7 + 43.4	15.7 ± 4.1
Duration of IVT, weeks	22.7 ± 5.3	23.7 ± 5.1	22.7 ± 5.3	23.7 + 5.1	22.7 + 5.3	23.7 + 5.1
Total cumulative dosage, mg	1281.2 ± 413.7	1942.7 ± 401.8	748.3 ± 151.3	304.8 ± 278.1	105.8 + 27.9	152.3 ± 33.2

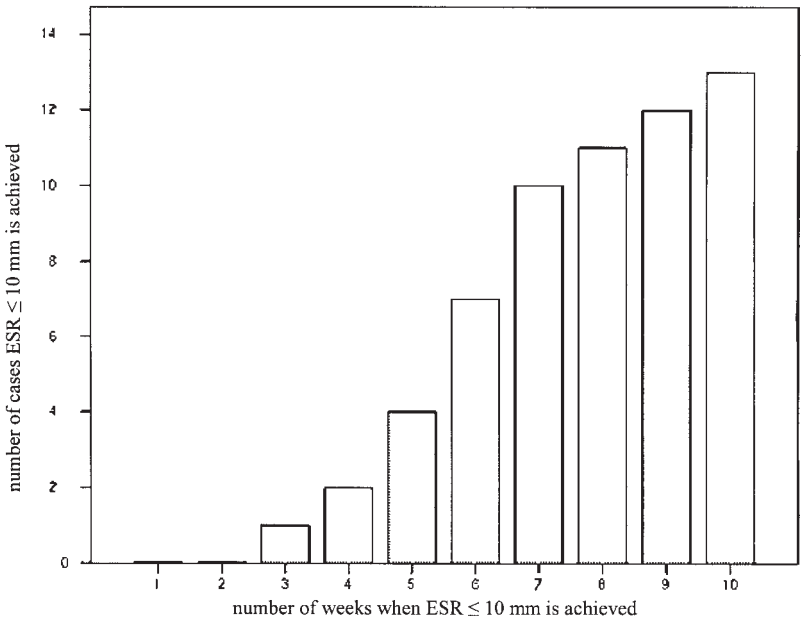

Figure 2. Achievement of ESR ≤ 10 mm from Weeks 3 to 10 in 60 cases of NSAID refractory AS treated with intravenous therapy of the SBC-5-IMN.

1 week and its suppression of < 1 month. Eleven patients in RwD and 15 in the RworalD group have undergone reinstitution of IVT for flare. Duration of RworalD was mean 4.6 ± 0.9 years. Flare occurred after mean 2.1 ± 0.5 years in 15/16 patients in the RworalD group. Flare rate per patient-year in patients in RworalD was 0.156. Duration of patients in RwD was mean 2.7 ± 0.9 years. Flare occurred in 11/44 patients after mean 3.7 ± 1.3 years in RwD. Flare rate per patient-year in RwD was 0.042. The reasons for flare are not clear, except flare was preceded by severe physical and/or mental stress. Early flare was reported within 1 week of onset. Suppression of flare to remission was achieved in mean 3.1 ± 0.9 weeks by reinstitution of IVT and weekly PA injection. The short period of 3.1 ± 0.9 weeks for suppression of flare did not significantly affect the mean duration of RwD of mean 2.7 ± 0.9 years and RworalD of mean 4.6 ± 0.9 years.

For clinical and laboratory variables between baseline and subsequent evaluations of those in the group with BASRI score < 2 the level of significance was $p \leq 0.025$, and in those in the BASRI ≥ 2 group it was $p \leq 0.01$, with significant distribution. For radiological variables between baseline and subsequent monitoring for both the patients with BASRI score < 2 and patients with BASRI ≥ 2 the level of significance was $p \leq 1.0$, i.e., the distribution was not significant (Table 4).

Adverse effects. Mild to moderate GI adverse effects were seen in 20/79 of the cases notwithstanding IVT sessions preceded by anti-emetics, spasmolytics, and proton pump inhibitors in those with history of GI symptoms. The latter included anorexia, nausea, vomiting, diarrhea, epigastric discomfort, and abdominal distention. In patients (BASRI ≥ 2 group) who had diabetes mellitus (n = 1), who developed corticosteroid induced hyperglycemia (n = 1), and those with his-

Table 4. Mean Bath Ankylosing Spondylitis scores at baseline of 79 cases, endpoint of 64 cases, and 15 dropouts after 6 years.

Status	Cases, Baseline BASRI < 2	Cases, Endpoint	p	Cases, Baseline BASRI ≥ 2	Cases, Endpoint	p
No.	54	44		25	20	
Hip pain	14	0		9	0	
BASRI-h	1.5 ± 1.3	0.1 ± 0.1	< 0.0001	2.8 ± 0.9	2.3 ± 0.6	> 0.05
BASRI-s	1.9 ± 0.4	0.1 ± 0.1	< 0.0001	2.1 ± 0.9	2.1 ± 0.6	> 0.05
ESR/male	99.7 ± 27.5	10.1 ± 2.2	< 0.0001	85.4 ± 35.7	8.1 ± 3.1	< 0.0001
ESR/female	97.9 ± 29.1	15.4 ± 2.6	< 0.0001	87.3 ± 33.9	13.6 ± 3.5	< 0.0001
CRP	214.7 ± 75.9	1.4 ± 0.3	< 0.0001	213.8 ± 66.9	1.9 ± 0.4	< 0.0001
BASDAI	6.19 ± 2.07	0.51 ± 0.15	< 0.0001	6.96 ± 1.53	0.83 ± 0.16	< 0.0001
BASFI	5.55 ± 1.91	0.70 ± 0.21	< 0.0001	5.91 ± 1.49	1.61 ± 0.32	< 0.0001
BASG	6.9 ± 1.7	0.9 ± 0.2	< 0.0001	7.3 ± 2.2	0.8 ± 0.2	< 0.0001
BASMI	2.31 ± 0.40	0.1 ± 0.1	< 0.0001	2.87 ± 0.70	1.5 ± 0.4	< 0.0001

tory of melena and/or hematemesis (n = 2), MPS was empirically replaced by 5FU (N = 4). Without IV MPS it took a significantly longer time and significantly more IV sessions to achieve ASAS 20, normalize the ESR and CRP, and reduce clinical Bath AS scores to < 1 (data not shown). MPS appeared to be a stronger IMN than 5FU. As all patients were refractory to physical therapy, daily or at least twice weekly swimming for the long term was obligatory only when ESR dropped to < 30 mm.

No patient dropped out due to resistant disease or inefficacy of the SBC-5-IMN. The early dropouts were due to noncompliance to the fixed and complex daily 5× weekly IVT and the fixed tapering schedules. No dropout qualified for secondary endpoint of ASAS 50 or ASAS 70 or remission. The ASAS 50, ASAS 70, RworalD, and RwD were attained in study cases, while no dropout achieved this status. No mortality was encountered among cases or dropouts. No conclusion could be drawn due to the small number of cases and dropouts. The health related quality of life and burden of disease were not recorded, except the costs of medications.

DISCUSSION

Therapy with SBC-5-IMN achieved dramatic and quick results in the majority of patients with NR-AS including: normal or negative CRP; normal ESR; ASAS 20; ASAS 50; ASAS 70; RworalD, RwD; radiological joint normalization, and remission; a large number of patients experienced prolonged remission after discontinuing therapy. Such results may be due to: intensive IVT; common receptor sites for immune suppression; IMN-naive status and BASRI score < 2 status of the vast majority of patients; early stage of disease with reversible changes; immediate suppression of early flare; interactive electronic doctor and patient communication; patient education; and possible spontaneous remission.

Our results may be accounted for as follows: Intravenous therapy achieves faster, maximum, and long-lasting efficacy with minimum adverse effects compared with oral therapy, which generates slow, minimum, and short-lasting efficacy with maximum adverse effects.

Although treatment of NR-AS with SBC-5-IMN was empirically initiated, a recent report seems to provide a molecular basis for this approach. Efficacy of the IVT is attributed to the combination of IV CYC with MPS/5FU, MTX[29], weekly PA[30], and corticosteroid infiltrations into sites of enthesitis. IVT, corticosteroid PA, and infiltration into enthesitis sites may share receptor sites for immunosuppression in systemic upstream and local downstream cytokine-dependent and cytokine-independent pathways. It is apparent that PA corticosteroid injection in RA shows equivalent efficacy as in NR-AS[14]. It is imperative that induction of remission be achieved in the shortest time possible before reaching BASRI score ≥ 2. This is to obtain RwD and radiological normalization of the axial and peripheral joints, which is impossible after BASRI > 2 is identified.

IV administration of CYC + MPS/5FU + MTX may suppress T cells and may indirectly inhibit activation of T cells + antigen-presenting cell complex via costimulatory pathways. This may have indirectly inhibited upstream systemic cytokine-dependent and cytokine-independent pathways in the secretion of cytokines and tumor necrosis factor-α (TNF-α) by macrophages, and autoantibodies by B cells. There may be no or fewer cytokines, TNF-α, and autoantibodies available to support local cytokine-dependent and cytokine-independent downstream pathways in the activation of synovial fibroblasts[31], osteoclasts, and chondrocytes[31-34]. Local inflammation may be reduced or terminated, and progression of joint damage most probably is slowed or stopped[18].

Concomitant weekly PA injection with DxM + TA may have directly suppressed local T cells, B cells, and macrophages. B cells seem to play several key roles in the development of synovitis[34,35]. This may have directly and indirectly suppressed local downstream cytokine-dependent and cytokine-independent pathways by inhibition of the production of local cytokines, TNF-α, and autoantibodies. Local

TA + DxM may indirectly inhibit activation of fibroblasts, osteoclasts, chondrocytes, and most probably may reduce or terminate joint inflammation and further joint damage. It may be summarized that SBC-5-IMN efficacy has common receptor sites in the suppression of upstream and downstream cytokine-dependent and cytokine-independent pathways.

Remission without drugs and RworalD are dependent on the BASRI score < or ≥ 2, and naivety to IMN. Only those with BASRI score < 2 and who were immunosuppressant-naive achieved RwD. That a large number of patients obtained prolonged remission without therapy may be related to their status of early AS with BASRI score < 2, IMN-naivety, and possibly to spontaneous remission. The importance of IMN-naivety cannot be underestimated: 4/20 cases of IMN non-naive patients with NR-AS and BASRI ≥ 2 did not achieve remission, while 16/20 cases with BASRI > 2, but who were IMN-naive, achieved RworalD.

When AS progresses to BASRI ≥ 2, radiological changes to treatment are not sensitive using BASRI-s and BASRI-h scores. Magnetic resonance imaging is evidently a more sensitive instrument for measuring response to therapy in AS in the short term[36].

Most probably the weekly PA corticosteroid injections may obviate the need for IV MPS, as 35% of the corticosteroids in the PA injections leaked into the systemic bloodstream[37]. In future therapies of patients with NR-AS the IV MPS can be replaced with 5FU, as 4 patients achieved remission with IV CYC + 5FU + MTX. The weekly PA injection did not affect glucose levels appreciably. This will avoid development of moon face, increased appetite and obesity, GI intolerance, dependency, and possible osteoporosis. We are not aware that the combination of IV CYC + MPS/5FU + MTX has been applied in NR-AS.

Using combinations of oral MMF 500 mg and CyS 50 mg twice or 3 times daily at only low doses is unlikely to achieve our study endpoints (see above). Moderate to severe NR-AS can only be suppressed by the IVT of the SBC-5-IMN plus PA injections. This is why oral drugs should be administered when ESR ≤ 20 mm (men ≤ 10 mm) and BASDAI < 1 have been achieved. Low dosages of oral drugs given empirically are effective in maintaining remission. The duration of IVT in patients with BASRI score < 2 was mean 22.7 ± 5.3 weeks, and in patients with BASRI ≥ 2 it was mean 23.7 ± 5.1 weeks. The total number of IVT sessions in the BASRI < 2 group was mean 36.5 ± 9.1 times, and in the BASRI ≥ 2 group it was mean 42.5 ± 10.9 times. The longest sessions in the BASRI < 2 and BASRI ≥ 2 groups were < 7 months.

In our study GI adverse effects were as high as with aspirin when GI protection is not provided. Currently GI adverse effects can be treated, minimized, or prevented. The high percentage of adverse effects may be due to common receptor sites in the GI tract for IMN side effects.

Because a combination of drugs was given, we cannot determine the relative percentage of each of the IMN contribution to efficacy and adverse effects. Immediate allergic reactions arising during IV drips may indicate the IMN concerned. Drug interactions between MPS/5FU, MTX, IV CYC, oral MMF, and CyS were not addressed in our study. However, combinations of oral MPS + MTX, MPS + CyS, or CyS + MTX are known to raise the other drug's concentration in the blood[13]. This may allow reduction of dosage of each IMN while achieving combined efficacy.

Apparently, low dosages of the IV combination of CYC + MPS + MTX do not affect the reticulo-endothelial and hematopoietic system appreciably, as no hematogenic adverse effects were encountered. Hematogenic safety of the SBC-5-IMN may be due to different receptor sites for induction of leukopenia, thrombocytopenia, anemia, or pancytopenia by each of the individual low-dose IMN. Low daily, weekly, and total cumulative dosages of the IMN, limited period of exposure, and limited weekly and total cumulative frequency of the IV sessions also may have contributed to the absence of dose-dependent liver, renal, cardiovascular, and hematogenic adverse effects of the SBC-5-IMN. Nevertheless, as the attachment of T cells by antigen-presenting cells (APC) and the subsequent activation of T cells + APC complex via costimulatory pathways are not permanently eradicated, the lifetime risk of flare remains. Blocking several of the multiple costimulatory pathways using abatacept after attachment of T cells by APC is still not the answer[38].

The fact that only a minority of patients achieve ASAS 70 using biologic DMARD (infliximab, etanercept, and adalimumab) may be due to only TNF-α being antagonized, leaving all the various types of cytokines and autoantibodies uninhibited to continue the chronic inflammatory process, as in rheumatoid arthritis[34]. Consequently, no normal levels of ESR, CRP, clinical remission, and radiological joint normalization and remission are reported in these studies[39,40]. After cessation of therapy with the biologic DMARD, almost all patients experience flare after several weeks to several months[41]. It is most probable that biological DMARD must be administered continuously or over a lifetime in most patients with AS to maintain continuous inactivation of TNF-α, which is incessantly produced by upstream macrophages and downstream T cells, macrophages, and B cells. Increased tolerance to the longterm application of the biologic DMARD requires increased dosages and increased costs. Inefficacy may be reduced by TNF-α –308 genotyping, as genotype G/G are better infliximab responders than are patients with A/A or A/G genotypes[42].

Using IV generic CYC, MPS/5FU, MTX, and oral MMF and CyS, the estimated first-year costs of treatment with the SBC-5-IMN is US$2000–3000. The second and third year cost is US$1000–2000 for oral drugs. In RwD there are no drug expenses after 3 years. Those in RworalD require longterm maintenance with MMF, which costs US$1000 annually. This is obviously less expensive than annual treatment costs with biologic DMARD of US$15,000–25,000 for

longterm or lifetime use[43]. Although the SBC-5-IMN is significantly less expensive than the biologic DMARD, it is still unaffordable and unavailable in many Third World countries. When a biologic DMARD is indicated and the patient cannot afford the costs, the SBC-5-IMN is a significantly less expensive, effective, and safe alternative.

When AS becomes refractory to physical therapy and to COX-1 and COX-2 NSAID, treatment with anti-TNF-α plus MTX achieved ASAS 20 in the majority of patients, but only a minority obtained ASAS 70. However, the majority of Third World countries cannot afford biologic DMARD. If an alternative treatment were available such as SBC-5-IMN, with excellent primary endpoint ASAS 20 and secondary endpoints ASAS 50, ASAS 70, and clinical and radiological remission, developing countries of Asia would reap the benefits.

As with all therapeutic agents in autoimmune disorders when irregularly applied for whatever reason, NR-AS becomes refractory to SBC-5-IMN.

SBC-5-IMN treatment guidelines were applied in rheumatoid factor-positive rheumatoid arthritis[18], rheumatoid and lupus vasculitis[44], and lupus nephritis with or without nephrotic syndrome[45], all with similar efficacy and side effect profile as in NR-AS. This may imply that in autoimmune diseases, IV CYC + MPS/5FU + MTX promote immunosuppression and inhibit secretion of TNF-α, cytokines, and autoimmune antibodies by suppressing T cells. Anecdotal success has been achieved in treating systemic scleroderma, psoriatic arthritis, reactive arthritis, adult Still's disease, etc., with similar efficacy and adverse effects.

In conclusion, step-down bridge combination therapy achieved ASAS 20, ASAS 50, and ASAS 70 in 64/79 and remission in 60/79 patients with NSAID-refractory AS. Controlled studies are needed to confirm the method and role of different drugs applied in our study in the developing countries of Asia, where the majority of patients with NSAID-refractory AS are unable to get treatment with TNF-α blockers.

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APPENDIX

Definitions

NSAID-refractory-AS. After treatment with at least 2 different NSAID over a period of at least 2 months, ASAS 20 is not obtained, and ESR, CRP, and BASDAI score do not improve, or worsen versus baseline.

Active disease. BASDAI ≥ 4, ESR ≥ 40 mm (men ≥ 30 mm), and CRP[9] ≥ 3 mg %.

Remission. ESR and CRP have declined to ≤ 10 mm (men ≤ 5 mm), and BASDAI, BASFI, BASG, and BASMI scores are mean < 1 (scale 0-10).

Remission with oral drugs. Remission is maintained with oral drugs.

Remission without drugs. Remission without drugs persists without flare.

Radiological normalization. BASRI ≥ 2 when normalization of the axial and/or peripheral joint(s) is obtained.

Radiological remission. BASRI ≥ 2 when progression of baseline calcification is terminated, erosion is healed, new erosion is prevented, and the following are at their baseline status: Spine: sclerosis, syndesmophytes; squared and fused vertebrae, and kyphosis. Hip joint: sclerosis, osteophytes; loss of joint space; bone on bone apposition; protrusio acetabuli; and bone deformity.

Dropout. Noncompliance with treatment schedules for any reason.

Flare. BASDAI rises to ≥ 1, ESR ≥ 20 mm (men ≥ 10 mm), and CRP ≥ 3 mg %.

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