

## Postgraduate Rheumatology Information for the Rheumatologists

### Breakthrough in the Treatment of NSAID-refractory Ankylosing Spondylitis by the Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants

John Darmawan, MD, PhD, FACR  
WHO Expert on Rheumatic Disease, Geneva, Switzerland  
Semarang, Indonesia

#### Introduction

In developed countries with health insurance and social securities (full financial support), it is hardly possible to get Ankylosing Spondylitis[1] (AS) into remission. In developing countries without health insurance and social securities (without financial support) talking about Remission may be inappropriate. Only very few in the third world can afford the Biologic Response Modifiers (Remicade = Infliximab; Enbrel = Etanercept; Kineret=Anakinra; Humira=Adalimumab; Mabtera=Rituximab). The Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants (SBP-6-IMNs) in the Therapy of NSAID-refractory AS (Nr-AS) is another novel but less expensive alternative. The SBP-6-IMNs comprises Intravenous (IV), Oral, and local (intraarticular & intralesional) therapy.

NSAID-refractory AS is defined when after treatment with at least 2 different NSAIDs over a period of at least 2 months, the Erythrocyte Sedimentation Rate (ESR)[2,3], C-Reactive Protein (CRP)[2,3,4], and BASDAI[5] Score do not improve or get worse significantly compared with baseline. COX1 and COX2 NSAIDs[6] and physical therapy have been the standard for treatment of Ankylosing Spondylitis (AS). Sulfasalazine shows only some variable beneficial effect in the peripheral joints in the short term[7]. NSAIDs neither stop or slow the progression of AS in NSAID-refractory AS, but have been associated with notorious gastrointestinal[8] and renal[9] toxicity with a high dropout rate. Methotrexate (MTX)[10,11], pulse intravenous (IV) Methylprednisolone (MPS)[12] and Cyclophosphamide (CyP)[13], oral Cyclosporine (CyS)[14] and Mycophenolate Mofetil[15] (MMF) in single drug therapy show varying efficacy in the treatment of AS. However, combination therapy may be required when treating AS with MTX[11].

#### The Objective

The objective of therapy with SBP-6-IMNs is suppression of the formation of autoantibody in autoimmune diseases. Suppression of the formation of autoantibody in autoimmune diseases is similar as in transplant patients. Low dosages of Cyclosporine (CyS) or Mycophenolate Mofetil (MMF) suppresses the formation of antibody against the transplanted organ.

In AS with high ESR, C-Reactive Protein (CRP) and high BASDAI Score (> 4), the autoimmune inflammation must be totally suppressed as soon as is possible. The IV therapy of the SBP-6-IMNs relatively fast suppresses the autoimmune inflammation with normalization of ESR, CRP, and BASDAI < 1, with Disease in Control (DiC) and subsequent Remission with oral Drugs (RworalDs) achieved.

Disease in Control is defined defined when after treatment with the SBP-6-IMNs, the CRP is < 3 mg/L, ESR < 25 in women and < 15 mm in men/1 hour, BASDAI < 1, BASFI[16] < 2\*, BAS-G[17] < 1 and BASMI[18] were significantly improved or not worse compared with baseline (p < 0.05). \*It is not possible to achieve BASFI < 1 in AS with BASRI 3-4[19,20].

Remission with oral Drugs (RworalDs) is defined when simiar status as in DiC is maintained with oral therapy of the SBP-6-IMNs for at least 2 years, provided early flares are immediately suppressed by re-institution of the IV therapy.

Flare is defined when axial or peripheral arthritis re-appeared in  $\geq 1$  joints with abnormal titer of CRP and ESR, and BASDAI > 1.

### **The Rationale**

The underlying rationale for early application of the SBP-6-IMNs in Nr-AS is based on the natural history of AS[21]: the disease shows continuous linear progression of radiological changes and over any period of 10 years progresses to 35%; radiological cervical spine progression is a function of: disease duration, severity of lumbar and hip involvement, and a history of iritis; a recent prospective observational study shows erosions have healed and continuous progressive radiological joint ankylosis has been terminated by the SBP-5-IMNs[22]; when irreversible joint damage occurs, the only option left is reconstructive axial and peripheral joint surgery or total peripheral joint replacement such as total hip and/or knee replacement.

### **Prognostic Factors**

The most important prognostic factor in Nr-AS is the treatment, grades of BASRI-s and BASRI-h independent of disease duration. Although the progression of the grade of BASRI-s and BASRI-h may evolve in the short to long term, the outcome of treatment is independent of disease duration. Short, medium, and long term Immunosuppressant-naïve NSAID-refractory AS can achieve Remission without Drug (RwD) as long as the BASRI-s and BASRI-h is < grade 2.

Remission without Drug (RwD) is defined when the oral therapy of Rworalds is tapered off over 1 year and after another year without drug and flare similar status as DiC is retained.

Early flare (within 1 week onset) during DiC, Rworalds, the 2 years period to RwD, and in RwD, must be immediately suppressed by reinstatement of the IV therapy. Only 1-2 weeks is required to suppress early flare and 1-2 months to taper off oral therapy. Full-blown flare requires the total schedules of the SBP-5-IMNs.

When ESR, CRP, and BASDAI are not normalized by therapy, the disease progresses from non-calcified AS (ncAS) to calcified AS (cAS) or from BASRI < 2 to BASRI  $\geq$  2. The autoimmune inflammation of calcified AS (cAS) can be suppressed to DiC and Rworalds, but not to RwD by the SBP-5-IMNs[22]. The best outcome is achieved in Immunosuppressant-naïve NSAID-refractory ncAS where RwD is feasible after 53.5-55.5 months of therapy with the SBP-6-IMNs.

### **Contra-indications**

The contra-indications for the application of single or combination drug therapy of Nr-AS with immunosuppressants such as IV CyC, MPS, 5FU, MTX, and oral MMF, and CyS are obvious. The inserted leaflets in the package of each individual immunosuppressant from the manufacturers are self-explanatory.

### **Exclusion Criteria**

Patients with a history of tuberculosis, hepatitis B or C, AIDS, Gout or another autoimmune disease, etc. excluded

### **Therapeutic Principle**

The therapeutic principle is to achieve total suppression of autoimmune inflammation (DiC) at the shortest possible period of time by the SBP-6-IMNs before BASRI  $\geq$  2 or calcification is seen on X-ray films (calcified AS=cAS). When the ESR is > 40 mm/1 hour Westergren (men > 30 mm) and BASDAI > 4 the SBP-6-IMNs is empirically applied in Nr nc and cAS to obtain DiC and Rworalds.

However, the individual variations of normal ESR can be baffling as in a few patients it can be normal or even subnormal with mild to moderate disease. This is in particular in chronic longstanding AS. After 1 week of therapy the ESR may rise to abnormal level before dropping to normal again or may even drop to subnormal level. Even normal level of ESR with a BASDAI of > 4 is an indication for therapy with the SBP-6-IMNs.

### **Methods**

The standard daily 5X weekly IV therapy comprises:

daily CyC + MPS + 5FU\* + weekly MTX + without oral corticosteroid (Methylprednisolone, Prednisone or Prednisolone).

Or CyC + 5FU\* + weekly MTX without IV MPS and oral corticosteroids Or

Intravenous weekly MTX is preferred because oral one has lower bioavailability[23]. The maximum number of daily intravenous sessions is 5 times per week to avoid high weekly cumulative dosages and adverse effects.

In CyC-refractory AS, Ifosfamide is an analog, which replaces CyC. In resistant cases, the patients are not immuno-naive anymore to IV CyC + MPS + weekly MTX. Nevertheless, these patients are still immuno-naive to the new IV combination of Ifosfamide + 5FU. This may induce remission again in CyC + MPS + weekly MTX-refractory AS (personal communication).

### **Intravenous Dosages**

1. CyC[24] 25-100 mg per session+
2. MPS[25]\* 0-125 mg per session
2. MTX[10,11]\*\* 5-15 mg per session once week +
3. 5FU\*\*\* 25-100 mg per session) +

The minimum dosages need to be applied in sensitive patients or in those with very low body weight (< 35 Kg). The sensitive patients may suffer adverse effects at the 100 mg dose of CyC and 5FU, 15 mg of MTX, and 125 mg of MPS, but not at the 75 or 50 or 25 mg of CyC, 5FU, or 5 mg MTX dosages respectively.

- \* Patients with Diabetes Mellitus and/or a history of melena and/or hematemesis are not given intravenous Methylprednisolone.
- \*\* Oral Folic Acid or Folinic Acid can be additional prescribed to minimize adverse effects of Methotrexate.
- \*\*\*based on empirical efficacy of 5FU in RH+ RA

Methylprednisolone is in fact not absolutely required to achieve DiC and Rworalds in Nr-AS, but relatively required to taper off and achieve DiC in patients still on oral corticosteroids at presentation. However, the combination of CyC+5FU+MPS+weekly MTX (SBP-6-IMNs) achieves: faster efficacy; reduces the total number of frequencies of intravenous sessions; tide over the dependency on corticosteroids the patients are still taking at presentation.

### **Tapering Off IV Therapy**

When the ESR dropped to < 40, < 30, and < 25 mm/hour (men < 30, < 20, and < 15 mm), the IV sessions is tapered to 3X, 2X, and 1X weekly respectively. After CRP is < 3 mg%, BASDAI < 1, and ESR is < 25 (women) or < 15 mm (men) Nr-AS achieves DiC. Then the IV session is tapered to once fortnightly, 4-weekly, 8-weekly and terminated. In some individual patients with long-term AS a final dose at 12 weeks maybe required.

### **Focal infection**

When normal ESR level has been achieved and the CRP is still abnormal then the source of chronic infections must be investigated. The negative CRP level is usually acquired within 1-2 months unless there is a chronic infection. A Panoramic View X-ray of the teeth should be taken, because most chronic focal infections are in the dental structures. Failing to find the source of the infection then intravenous or oral derivates of the broad spectrum Cephalosporines can be given to lower resistant CRP level.

### **Oral Therapy**

#### **The oral therapy of the SBP-6-IMNs comprises:**

1. Methotrexate 5-15 mg per week when the intravenous therapy is terminated[10,11] +
2. Cyclosporine (CyS)\* 50 mg bid-tid[14].
3. MMF[15] 500 mg bid-tid +

\*MMF and CyS have been prescribed for > 10 years in transplant patients with acceptable efficacy and tolerable adverse effect.

Oral therapy initiated in combination with the intravenous therapy should be continued for at least 2 years after termination of the IV therapy. This is to consolidate and maintain the normal ESR and CRP, and

BASDAI of < 1 during the period of in Rworalds. Consequently, this stabilizes or consolidates the status of Rworalds.

The oral therapy of MMF+CyS+MTX in the dosages low enough to avoid adverse effects is effective only when the ESR and CRP are normal, and BASDAI is < 1. The oral therapy is initiated together with the intravenous therapy for initial loading and obtaining a minimum effective blood level by the time ESR and CRP is normal and stabilized, BASDAI is < 1, and IV therapy is terminated[22].

Trying to suppress the autoimmune inflammation of Nr-AS with an ESR of more than 40 mm/1 hour (> 30 mm/1 hour in men), CRP > 3 mg%, and BASDAI > 4 by low dose oral immunosuppressive combination therapy is inclined to fail, at least at the low oral dosages of CyS + MMF + MTX applied within the limit without adverse effects.

No oral Cyclophosphamide[26] and Methylprednisolone[27] are prescribed for reasons of more severe and more frequent adverse effects compared with intravenous administration. Long-term oral corticosteroids is harmful to the kidneys in Lupus Nephritis[28]. This would hold true for all patients with autoimmune diseases as in Nr-AS. The IV 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.

### **The schedules to Remission without Drug in immunosuppressant-naïve NSAID-refractory AS with BASRI < 2.**

1-2 months daily IV therapy (limited to 5 sessions per week)

1-2 months declining frequency of IV sessions to normal CRP, ESR, and BASDAI < 1\*

3.5 months Disease in Control for tapering off IV therapy\*

2 years consolidation in Remission with oral Drugs

1 year tapering off oral drugs.

1 year without drug and flare - Remission without Drug is achieved

It takes 2-4, 5.5-7.5, and 53.5-55.5 months to achieve Disease in Control, Remission with oral Drugs, and Remission without Drug respectively.

\*In exceptional cases with longstanding disease duration (> 1-2 decades of moderate and mild active disease) the 5X weekly IV sessions needs to be continued without declining frequency until DiC is acquired.

### **Monitoring of Adverse Effects**

Adverse effects are daily and cumulative dose-dependent. The daily dosages of IMNs are low enough not to induce serious adverse effects. The daily intensive intravenous immunosuppression successively 5X weekly session lasts only mean 1-2 months. As Rworalds is attained after 7.5 months by IV therapy of the SBP-6-IMNs, the total cumulative dose and period of exposure to IV therapy is limited. This has prevented serious adverse effects, except gastrointestinal (GI) ones[22].

### **Prevention of gastrointestinal adverse effects**

Preceding the IV therapy with intravenous Granisetron (Kytril), H<sub>2</sub> Antagonists and/or Proton Pump Inhibitor, antiemetic, and spasmolytic has minimized the GI adverse effects. Mild GI adverse effects were 55.5% in an open label observational study with the first preliminary SBP-5-IMNs[29], but only 25.0 in the application of the second version of the SBP-6-IMNs[22]. This was achieved by intensification of prevention of gastrointestinal adverse effects such as anorexia, nausea, vomiting, and diarrheas. H<sub>2</sub> Antagonist and/or Proton Pump Inhibitors intravenous drips preceded those with a previous history of gastrointestinal ulcer and bleeds. Emerging anorexia, nausea and vomiting induced by IV IMNs are suppressed and prevented by Granisetron. Monitoring of adverse effects by standard laboratory procedures of the combination of IMNs should be carried out at least once monthly. When indicated anytime during the period of the IV therapy.

#### Hematological monitoring of adverse effects and dosages of the Immunosuppressants

Leucocytes	Thrombocytes	Hematocrit	CyC + MTX + %FU	MPS
> 4000	> 100,000	> 35	100%	100%
4,000-2,500	100,000-50,000	30-35	50%	100%
< 2,500	< 50,000	< 30	0%	100%

Very rare hematological adverse effects of the SBP-6-IMNs can be overcome:

1. Leucocytes < 1000 by daily intravenous Filgrastim (Neupogen)
2. Hematocrit < 25 by Subcutaneous Recombinant Human Erythropoietin (Recormon).
3. Thrombocytes < 50,000 by intravenous drips in the dilution of 0.1-0.5 CC Epinephrine in 100-200 CC 0.9% NaCl[29] + IV MPS

When Pancytopenia occurs, the SBP-6-IMNs must be suspended in the meantime while sub 1, 2, and 3 should be administered together until the number of blood cells is normalized. Rechallenge with the SBP-6-IMNS may be attempted, by increment of the number of the IMN one by one albeit in lower dosages.

Leukocyte and thrombocyte counts of 500/1 CC and 2000/1 CC (including Idiopathic Thrombocytopenic Purpura = ITP) and hemoglobin of 2.5 mg% (lupus hemolytic anemia) have been normalized by these agents in conjunction with the SBP-6-IMNs without transfusion of leucocytes, thrombocytes, and erythrocytes. The reasons are that transfused thrombocytes, leucocytes, and erythrocytes are destroyed within 1 week by the antibodies.

#### **Prevention of Dropouts because of Allergy**

A history of previous allergy or allergy appearing during intravenous therapy to any or all the drugs applied, must be preceded by intravenous drips of the dilution of 0.1-0.5 CC Epinephrine in 100-200 CC 0.9% NaCl. The very slow drip-rate depends on the appearance of palpitation (tachycardia)[29] and discomfort of the patients. All the contraindications and safety precautions must be observed before the administration of intravenous Epinephrine. Allergy appearing during intravenous therapy, identical dilution of Epinephrine can be inserted between the sequence of serial drugs, while temporary stopping the cause of the allergy. After the Epinephrine is infused then the cause of the allergy can be safely re-administered again. This has been daily routine procedure in the Indonesia Rheumatic Center in Semarang.

#### **Intraarticular and Intralesional Injections**

The local injections consists of the Local Combo of 3 drugs. Intraarticular injections for persistent chronic arthritis and intralesional injections for enthesitis, bursitis, tendonitis, and/or Fibromyalgia Syndrome (here is Fibromyalgia a complication of AS) should be applied concomitantly with the intravenous + oral therapy. In particular hip arthritis and persistent tendo-muscular pain from enthesitis or Fibromyalgia require local injections with the cocktail. The cocktail contains Lignocain 20%, Dexamethasone 20%, and depo Triamcynolone 60%. Efficacy of Lignocain is direct and lasts 4 hours, Dexamethasone efficacy commences after 4 hours and lasts 4 days, and depo Triamcynolone effect starts after 4 days and last at least a fortnight. Some experience is required to feel the painful and tough tendon of enthesitis and painful tiny knobby focal points of Fibromyalgia.

#### **Co-morbidity**

Co-morbidity or associated conditions such as Hypertension, Diabetes Mellitus, Artherosclerosis, Neuropathy, Osteoporosis, etc., must be treated simultaneously with the Nr-AS. Osteoporosis can be due to corticosteroids abuse or menopause, or advanced age (> 60-70 years), or Nr-AS or immobility or any one, two, three or all four factors combined. Intravenous Zoledronic Acid[30] with concomitant daily oral Calcium and Minerals supplements can treat osteoporosis faster than oral Biphosphonates. Complications such as Vasculitis, Irritable Colon, Retinopathy, Irridocyclitis, etc., must be treated concomitantly

#### **Dropout**

Dropout is defined for the treated cases who do not complete the SBP-6-IMNs for any reason. Dropouts never achieve DiC, Rworalds, and Rwd, but nevertheless, considerable improvements still occur in these irregular treated patients[22].

### **Outcome Measures**

Besides the clinical outcome measures such as BASDAI, BASFI, BASG, and BASMI, the BASRI-s[19] and BASRI-h[20] are applied at baseline and every 2 years to monitor radiological changes[31].

The SBP-6-IMNs in the Therapy of AS is applicable to almost all other Autoimmune Disorders. Almost all the cases with autoimmune inflammation such as Rheumatoid Factor Positive Rheumatoid Arthritis[32], Biopsy-proven Lupus Nephritis[33], NSAID-Refractory Reactive Arthritis, Psoriatic Arthritis, Systemic Progressive Scleroderma, etc, can be brought into DiC and Rworalds. At early stadium Rwd is achieved by this immunosuppressive combination therapy[22,29,33]. In Systemic Progressive Scleroderma it takes at least 2 year before the skin texture is normalized by the oral therapy after termination of IV therapy (personal communication). The SBP-5-IMNs and SBP-6-IMNs are most effective in immunosuppressant-naïve patients with ncAS disease.

### **Summary**

High level of ESR, CRP, and BASDAI  $> 4$  indicates activity and severity of the disease and correlate with outcome of AS. Suppression of ESR and CRP to normal, and BASDAI to  $< 1$  by the SBP-6-IMNs inactivates the disease clinically and radiologically[22]. Intravenous combination of CyC+MPS+MTX or CyC+5FU+MTX or CyC+5FU+MTX+MPS serves to normalize the ESR and CRP, and suppress the BASDAI to  $< 1$  in a relatively short period of time. The oral combination of MMF+CyS+MTX serves to maintain the normal level of ESR, CRP and BASDAI  $< 1$  achieved by the IV therapy. Mild gastrointestinal adverse effects are common, but the dreaded hematological, renal, and liver ones are exceptional rare or not encountered. Hematological toxicities are easily normalized by Filgrastim (leucopenia), Recombinant Human Erythropoietin (severe anemia), and diluted solution of Epinephrine (thrombocytopenia). Dose and time dependent adverse effects are minimized by limitation of the total cumulative dose over the limited period of IV therapy and the limited weekly cumulative dose. Remission with oral drugs in cAS has been obtained and in ncAS Remission without Drug has been achieved[22].

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**This protocol is an ever evolving initiative, which requires a dynamic continuous assessment, refinement, and revision based on new experience gained in open-label or inception cohort observational studies and in Randomized Controlled Trials (RCT).**

In AS which is NSAID-refractory (COX1/COX2) and DMARDs-combination- refractory (low dose Prednisone + Hydroxychloroquine + Sulfasalazine + Methotrexate), or Biologic Response Modifier + Methotrexate-refractory (Infliximab + Methotrexate-refractory or Etanercept + Methotrexate-refractory), this Treatment rotocol is worthwhile trying. You will be surprised with the excellent short, medium, and long-term outcome and minimum adverse effects encountered[22].