

## Postgraduate Rheumatology Information for the Rheumatologists

### Breakthrough in the Treatment of biopsy-proven Lupus Nephritis by the Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants

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#### Introduction

Inadequately treated biopsy-proven Lupus Nephritis (bpLN)[1] in WHO Class III, IV, and V is inclined to progress to Nephrotic Syndrome[1], WHO Class VI renal biopsy, End Stage Renal Disease (ESRD), and mortality by infections. However, therapy of LN has achieved Remission without Drug (RwD) or Treatment-free Remission[2,3,4,5]. In LN, renal damage is a predictor of further damage in the renal and other organs[6]. Biopsy-proven LN is an emergency situation and must be immediately, appropriately, and adequately treated. Inadequately treated, renal and other organs damage by LN progresses within a few years to multiple organs in an irreversible state. Early diagnosis and treatment improved clinical outcome of LN[7].

#### The Objective

The objective of the Step-down Bridge Protocol of Intravenous (IV) and Oral Combination of 6 Immunosuppressants (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. The SBP-6-IMNs comprises Intravenous (IV), Oral, and local (intraarticular & intralesional) therapy.

The IV therapy consists of Cyclophosphamide (CyC), 5-Fluorouracil (5FU), Methylprednisolone (MPS), and weekly Methotrexate (MTX). The Oral Therapy is to stabilize and maintain Disease in Control (DiC) and Remission with oral Drugs (RworalDs). Oral therapy is a combination of Mycophenolate Mofetil (MMF), Cyclosporine (CyS), and weekly MTX when the frequency of IV therapy is reduced to once fortnightly. Local therapy composes of the combination of Triamcynolone 60%, Dexamethasone 20%, and Lignocain 20%.

In LN with ESR of  $> 40$  mm/1 hour Westergren (men 30 mm) and the (SLAM Score)[8]  $> 4$ , the SBP-6-IMNs is empirically applied. When LN is biopsy-proven in WHO Class 3,4, and 5 with Systemic Lupus Activity Measure Score (SLAM Score) of  $> 4$  and Erythrocyte Sedimentation Rate (ESR)  $> 40$  mm, the SBP-6-IMNs is immediately empirically applied. The IV therapy relatively fast suppresses the autoimmune inflammation with normalization of ESR and SLAM Score to  $< 1$  and DiC is achieved.

**Disease in Control** is defined when the mean SLAM Score is suppressed to  $< 1$  and ESR  $< 25$  mm (men  $< 15$  mm) and this status is consolidated by oral CyS + MMF + Methotrexate/wk during 3.5 months tapering of IV therapy.

**Remission with oral Drugs** is defined when the mean SLAM Score and ESR are maintained in similar status as in DiC by oral therapy. The RworalDs is consolidated for at least 2 years by immediate suppression of early flare by reinstatement of IV therapy. Thereafter, oral therapy is tapered off over a period of 1 year. If 2 flares appear during repeated tapering of oral drugs, RworalDs should be maintained in short to medium and long-term.

#### The Rationale

The underlying rationale for early application of the SBP-6-IMNs in bpLN is: once renal damage occurs, progressive damage ensues when disease activity remains high (SLAM Score > 4); inadequately treated other organs are additionally progressively affected beside the kidneys such as Lupus Pericarditis with effusion, Lupus Myocarditis, Lupus Pleuritis with effusion, Pulmonary Lupus, Extremities and Digital Vasculitis, Neuropsychiatric Systemic Lupus with Cerebrovascular accident; significant continuous progression of renal damage occurs over 15 years when LN is treated with oral corticosteroids[9]; initial high ACR Damage Index is associated with high mortality rate[10]

### **Prognostic Factors**

The most important prognostic factors in LN are: early diagnosis and early treatment[7]; Chronicity Index 5[11]; renal biopsy WHO Class III, IV, and V[11]. WHO Class I and II do not require SBP-6-IMNs treatment and Class VI is irreversible histological damage, when nothing helps. The best outcome is achieved in Immunosuppressant-naïve bpLN where DiC, Rworalds, and ultimately RwD is achieved after < 4.5 years. The SBP-6-IMNs in the therapy of LN is most effective in IMN-naïve patients with high activity index (> 4) and low chronicity index (< 5).

**Immunosuppressant-naïve to SBP-6-IMNs** is defined for patients who have never been exposed to any of the drugs in the IV and oral drugs of the SBP-6-IMNs.

**Flare** is defined when the SLAM Score raises to > 1 and ESR > 25 mm. Early flare (within 1 week onset) during DiC, Rworalds, tapering off oral therapy, 1 year without drug and flare, and RwD must be immediately suppressed by reinstatement of the SBP-6-IMNs. Only 1-2 weeks is required to suppress early flare and 2-3 months to taper off oral therapy again to RwD. Full-blown flare requires the total schedules of the SBP-6-IMNs.

### **Remission without Drug**

Remission without Drug is defined when identical status as DiC is maintained after oral therapy is tapered off over a period of 1 year with a subsequent year without drug and flare.

### **The schedules to achieving RwD are:**

- 1-2 months daily IV therapy (limited to 5 sessions per week to avoid adverse effects from weekly cumulative dosages)
- 1-2 months declining frequency of IV sessions to DiC
- 3.5 months DiC during tapering off IV therapy when IV MTX/wk is switched to Oral-MTX/wk
- 2 years consolidation of Rworalds
- 1 year tapering off oral therapy.
- 1 year without drug and flare acquires RwD

The period required to achieve RwD is 53.5- 55.5 months or < mean 4.5 years.

### **Therapeutic Principle**

The therapeutic principle is to achieve total suppression of autoimmune inflammation (DiC) at the shortest possible time by the SBP-6-IMNs. This must be achieved without serious adverse effects and before irreversible kidney damage (renal biopsy WHO Class VI) appears.

### **Contra-indications**

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

### **Methods**

The standard daily 5X weekly intravenous immunosuppressive combination therapy comprises: daily CyC + MPS + 5FU plus weekly MTX without oral corticosteroid (Methylprednisolone, Prednisone or Prednisolone). Intravenous weekly MTX is preferred because oral one has lower bioavailability[12]. The maximum number of daily intravenous sessions is 5 times per week to avoid high weekly cumulative dose and adverse effects. In CyC-refractory bpLN, Ifosfamide is an analog, which replaces CyC.

### **Intravenous Dosages**

1. MPS[13] 25-125 mg per session
  2. CyC[13] 25-100 mg per session+
  2. MTX\* 5-15 mg per session once week +
  3. 5FU\* 25-100 mg per session) +
- \*empirical application based on efficacy in RF+ RA

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, 5FU, 15 mg MTX, and 125 mg of MPS, but not at the 75 or 50 or 25 mg or 5 mg MTX dosages. These low dosages are still effective because these patients are sensitive to the efficacy of these IMNs.

- \* Oral Folic Acid or Folinic Acid can be additional prescribed to minimize adverse effects of MTX
- \*\*Patients with Diabetes Mellitus and/or a history of melena and/or hematemesis are not given intravenous Methylprednisolone. Instead the combination of IV CyC + 5FU + MTX is given.

Methylprednisolone is in fact not absolutely required to achieve DiC, but relatively required to taper off oral corticosteroids at presentation. However, the combination of CyC+5FU+MPS+weekly MTX achieves: faster DiC; reduces the total number of frequencies of intravenous sessions; tide over the dependency on existing oral corticosteroids at presentation. It is possible to terminate directly the oral corticosteroids at presentation and switch over directly to IV MPS + CyC + 5FU + MTX.

### **Tapering off IV Therapy from the SBP-6-IMNs**

After ESR dropped to < 40, < 30, and < 25 mm/hour (men < 30, < 20, and < 15 mm), the IV sessions are tapered to 3X, 2X, and 1X weekly respectively. When ESR is < 25 (women) or < 15 mm (men) bpLN acquires DiC. During DiC, the IV session is tapered to once fortnightly (in conjunction of switching IV to oral weekly MTX), 4-weekly, 8-weekly and then terminated to Rworalds. In some individual patients with bpLN a final dose of IV CYC+MTX+MPS+FU at 12 weeks maybe required.

### **Oral Therapy**

Oral therapy comprises:

1. Mycophenolate Mofetil (MMF)\* 500 mg bid-tid[14] +
2. Methotrexate 5-15 mg per week +
3. Cyclosporine (CyS)\* 50 mg bid-tid[15].

\*MMF and CyS have been safely prescribed for > 10 years in transplant patients.

Oral therapy is initiated concomitantly with the IV therapy. This is to consolidate and maintain DiC during the period of tapering off IV therapy and subsequent Rworalds. Consequently, this stabilizes or consolidates the status of Rworalds.

The oral therapy in the dosages low enough to avoid adverse effects is effective only when the ESR and CRP are normal. The oral therapy is initiated together with the IV therapy for initial loading and obtaining a minimum effective blood level by the time ESR is normal and stabilized and IV therapy is terminated.

Trying to suppress the autoimmune inflammation of BpLN SLAM Score of > 1 and ESR of more than 40 mm/1 hour by low dosages of oral MMF+CyS+MTX is inclined to fail, at least at the low oral dosages of these IMNs applied within the limit without adverse effects.

No oral MPS[16] and CyC[17] are prescribed for reasons of more severe and more frequent adverse effects compared with intravenous administration. 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.

### 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 1-2 months. As Rworalds is attained after 5.5-7.5 months by IV therapy, the total cumulative dose and period of exposure to IV therapy is limited. This has prevented serious adverse effects, except gastrointestinal (GI) ones.

### Prevention of gastrointestinal adverse effects

Preceding the IV therapy with intravenous Granisetron, 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[18], but only 25.0 in the second SBP-6-IMNs[19]. 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<sup>22</sup> + IV MPS

When Pancytopenia occurs, IV and oral therapy must be suspended 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 dropout due to 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)[20] 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 a routine procedure in the Indonesia Rheumatic Center in Semarang.

### Intraarticular and Intralesional Injections

The local injection 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 last 4 hours, Dexamethasone commence after 4 hours and last 4 days, and depo Triamcynolone 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.

### **Additional therapies in Nephrotic Syndrome**

1. Generalized edema due to excess body fluids because of hypoalbuminemia should be immediately removed by daily IV infusion of human albumin to at least minimum normal level.
2. Pericardial, pleural, and abdominal effusion will be excreted by the kidneys when the serum albumin has achieved normal level. Furosemide facilitates fluids excretion in the urinary tract
3. Mineral imbalance should be immediately restored by IV drips of modified Ringer's Solution
4. Uremia can be lowered by essential ketoacids (Ketosteril)
5. Autoimmune pericarditis and pleuritis will be totally suppressed by the IV therapy in a relative short period of time.
6. Intravenous administration of roborantia and nutrition are required when the patient cannot take oral or nasogastric fluids and nutrition.

### **Co-morbidity**

Co-morbidity or associated conditions such as Hypertension, Diabetes Mellitus, Atherosclerosis, Neuropathy, Osteoporosis, etc., must be treated simultaneously with the LN. Osteoporosis can be due to corticosteroids abuse or menopause, or advanced age (> 60-70 years), or SLE or immobility or any one, two, three or all four factors combined. Intravenous Zoledronic Acid[21] with concomitant daily oral Calcium and Minerals supplements can treat osteoporosis faster than oral Biphosphonates when the Tscore is > 4. 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 therapy protocol for any reason. Dropouts never achieve DiC, Rworalds, and Rwd.

### **Outcome Measures**

The choice of Outcome Measures is left to the discretion of the main investigator. Besides the SLAM Score, the other 5 outcome measures can be applied as desired[8].

Almost all the cases with autoimmune inflammation such as Rheumatoid Factor Positive Rheumatoid Arthritis[18], NSAID-Refractory Reactive Arthritis, NSAID-Refractory Ankylosing Spondylitis[22], Psoriatic Arthritis, Systemic Progressive Scleroderma, etc, can be brought into Remission with oral Drugs. At early stadium Remission without Drug is achieved by this immunosuppressive combination therapy[3,19]. The SBP-6-IMNs is applicable to almost all other Immunosuppressant-naïve Autoimmune Disorders including Amyotrophic Lateral Sclerosis, Multiple Sclerosis, and Alzheimer's Disease.

### **Summary**

High level of ESR indicates activity and severity of the disease and correlate with outcome of bpLN. Suppression of ESR to normal by "SBP-6-IMNs in the therapy of bpLN," inactivates the disease clinically. The IV therapy serves to normalize the ESR and SLAM Score in a relatively short period of time to DiC. The oral therapy serves to maintain Rworalds achieved by the IV therapy. 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, Recombinant Human Erythropoietin, and diluted solution of Epinephrine. Dose and time dependent adverse effects are minimized by limitation of the total and weekly cumulative dose over the limited period of IV exposure IMNs. Remission with oral drugs and ultimately Rwd have been achieved.

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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).**