

## Postgraduate Medical Information for the Medical Practitioners

### Breakthrough in the Treatment of biopsy-proven Lupus Nephritis 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

#### Frequent Asked Questions

##### **When your Lupus Nephritis (lupus of the kidneys) is confirmed by renal biopsy. What are the best treatment options?**

Biopsy-proven Lupus Nephritis is an emergency situation. Immediate, appropriate, and adequate treatment must be given as soon as it is possible. The best treatment option is by the Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants (SBP=6=IMNs).

##### **In the short term (< 5 years).**

In the short term Lupus Nephritis must be controlled (Disease in Control) before irreversible damage occurs in the kidneys and other organs (Chronicity Index > 5 Lupus Prognosis Index > 5). This can be achieved by treatment with the SBP-6-IMNs.

##### **What is the SBP-6-IMNs?**

The **SBP-6-IMNs** comprises Intravenous (IV) Cyclophosphamide + Methylprednisolone + 5-Fluorouracil + weekly Methotrexate and oral Mycophenolate Mofetil + Cyclosporine + weekly Methotrexate when the IV therapy is terminated. Oral Methotrexate and Cyclosporine are optional, because Mycophenolate Mofetil can maintain the majority of patients in Remission with oral Drug alone (Cellcept) for short, medium, and long term.

##### **The schedules of the SBP-6-IMNs application in patients with Lupus Nephritis**

1. Initially, intensive daily application of the SBP-6-IMNs is limited to 5X weekly for 1-2 months to avoid weekly cumulative dose-dependent adverse effects.
2. Declining frequency of intravenous therapy to 3, 2, and once weekly in accordance with the declining ESR levels of < 40 mm, < 30 mm, and < 25 mm respectively for 1-2 months
3. After ESR is suppressed to < 20 mm (men < 10 mm) per 1 hour with the mean Systemic Lupus Activity Measure Score (SLAM Score) < 1, Disease in Control is achieved. During Disease in Control the IV therapy is tapered off in 3.5 months.
4. After the IV therapy is terminated, Remission with oral Drugs must be maintained for at least 2 years.
5. During the 3<sup>rd</sup> year Oral Therapy should be tapered off. When 2 repeated attempts to taper off oral drugs induce flares then the patient should remain in Remission with oral Drugs for short (< 5 years), medium (5-10 years), and long term (> 10 years).
7. When the oral drugs are tapered off, Remission without Drug is achieved

Early flare during Disease in Control (identical with Remission under intravenous and oral therapy), Remission with oral Drugs over a 2 years period, the 1 year period of tapering off drugs, and Remission without Drug must be immediately suppressed by the SBP-6-IMNs.

**Why are early flares so responsive to retreatment with the IV therapy of the SBP-6-IMNs?**

In whatever early diseases when adequately and appropriately treated the outcome is excellent

**Disease in Control** is defined when the SLAM Score is  $< 1$ , and the ESR is normalized by treatment with the SBP-6-IMNs.

**Remission with oral Drugs** is defined when the IV therapy is tapered off during Disease in Control and similar status is maintained by oral therapy for at least 2 years.

**Remission without Drug** is defined when the oral therapy is tapered off over a period of 1 year with similar status retained as in Remission with oral Drugs.

**Flare** is defined when the SLAM Score becomes  $> 1$  with abnormal levels of ESR.

**Early flare** is defined when its onset is less than 1 week ago.

What is the shortest and longest period to obtain Disease in Control in patients with Lupus Nephritis?  
2-4 months

**How long does it takes to obtain Remission with oral Drugs?**

5.5-7.5 months

**How long does it takes to acquire Remission without Drugs?**

3.5 - 4.5 years

**What happens if for whatever reasons the patient with Lupus Nephritis cannot keep the tight schedules of the SBP-6-IMNs?**

Even under the tight treatment schedules of the SBP-6-IMNs, it is still extremely difficult to achieve Disease in Control and Remission with oral Drugs. This is in particular so in not immunosuppressant-naïve patients.

**What is meant by not Immunosuppressant-naïve to the SBP-6-IMNs?**

Not Immunosuppressant-naïve to the SBP-6-IMNs is defined for patient who has been exposed to treatment with IV Cyclophosphamide + Methylprednisolone + 5-Fluorouracil + weekly Methotrexate and oral Mycophenolate Mofetil + Cyclosporine. If any of the 6 drugs from the SBP-6-IMNs has been prescribed intermittently then the patient is not Immunosuppressant-naïve.

**What happens if the patient can only attend the IV sessions on a hit and run basis?**

This has been done by most of the patients for whatever reasons. The patient can feel when she is in a critical condition and her mother can see that too when the SLAM Score is  $> 5$  and the ESR  $> 80$  mm. The oral prednisone or Prednisolone, or Methylprednisolone (corticosteroids) is not helping when the ESR is over the 80 mm/1 hour unless taken daily in very high dosages ( $> 40$ -100 mg equivalent dosages of Methylprednisolone). Obviously, this very high oral dosage of corticosteroid is very quickly detrimental to the health of the patients. These patients usually come for the IV therapy and disappear for whatever reasons when the ESR is suppressed to  $< 40$  mm. Under ESR of  $< 40$  mm the patient can do reasonably well in her daily activities of living supported by the oral prednisone or Prednisolone, or Methylprednisolone.

**Oral Prednisone or Prednisolone or Methylprednisolone is a standard first line drug given to all lupus patients. Why it is not in the SBP-6-IMNs?**

Ultimately, the patient with Lupus Nephritis may end up with renal dialysis if oral corticosteroids are used for long term ( $> 20$  years) therapy. Conclusion of the publication below underline the risk taken when corticosteroids is continued long term for therapy of Lupus Nephritis.

Significant continuous progression of renal damage occurs over 15 years when Lupus Nephritis is treated with oral corticosteroids\* (Prednisone or Prednisolone or Methylprednisolone).

\*Gladman DD, Urowitz MB, Rahman P, Ibanez D, Tam LS. Accrual of organ damage over time in patients with systemic lupus erythematosus. *J Rheumatol.* 2003 Sep;30(9):1955-9.

**What happens if this erratic treatment behavior is repeated on and off in the short term?**

Ultimately, the SBP-6-IMNs is not effective anymore and the patient progresses to Pulmonary Lupus and/or Neuropsychiatric Lupus and/or renal biopsy of WHO Class VI, which all induces a short survival rate for the patient.

**Who can obtain Remission without Drug by the SBP-6-IMNs?**

Only Immunosuppressant-naïve patients with Lupus Nephritis and Chronicity Index of < 5 Lupus Prognosis Index of  $\leq 5$  can achieve Remission without Drug.

**How long can Remission without Drug lasts?**

Remission without Drug can last long term or lifetime, provided early flare is immediately suppressed within the 1<sup>st</sup> week of onset by the SBP-6-IMNs.

**2. In the medium term (5-10 years)**

- Those patients who are not immunosuppressant-naïve with Chronicity Index > 5 or Lupus Prognosis Index > 5 do not obtain Disease in Control and Remission with oral Drug. Nevertheless, considerable improvements are still acquired by these patients.
- Those patients who are not Immunosuppressant-naïve with Chronicity Index of < 5 or Lupus Prognosis Index  $\leq 5$  acquire Remission with oral Drugs.
- Those patients who are Immunosuppressant-naïve but with chronicity Index of > 5 cannot attain Disease in Control and Remission with oral Drugs.
- Those patients who are Immunosuppressant-naïve but with chronicity Index of < 5 or Lupus Prognosis Index  $\leq 5$  attain Remission without Drug within 5 years.
- Remission with oral Drugs is sustained through medium term if early flares are immediately suppressed by the SBP-6-IMNs.
- Remission without Drug is sustained through medium term if early flares are immediately suppressed by the SBP-6-IMNs.

**3. In the long-term (> 10 years)**

Remission with oral Drugs is sustained through long-term or lifetime if early flares are immediately suppressed by the SBP-6-IMNs.  
Remission without Drug can be sustained long term or lifetime when any early flare is immediately suppressed by the SBP-6-IMNs.

**What is the outcome of the treatment of Lupus Nephritis by the SBP-6-IMNs?**

In the short term

Disease in Control

Remission with oral Drugs

Remission without Drug

In the medium term

Maintenance of Remission with oral Drugs by reinstatement of the intravenous therapy whenever flare appears

Sustaining Remission without Drug by immediate suppression of early flares with the SBP-6-IMNs

In the long-term

Maintenance of Remission with oral Drug by reinstatement of the intravenous therapy whenever flare appears

Sustaining Remission without Drug by immediate suppression of early flares with the SBP-6-IMNs

**What are the gastrointestinal toxicities of the SBP-6-IMNs?**

Anorexia, nausea, vomiting, gastric discomfort, and diarrheas are the gastrointestinal toxicities. Preceding IV infusion with Granisetron (Kytril), H2 Antagonists and/or Proton Pump Inhibitor, antiemetic and spasmolytic, easily prevents these symptoms and signs.

**What are the blood toxicities of the SBP-6-IMNs?**

In the low dosages applied no blood toxicities are encountered. If ever Leukopenia or Thrombocytopenia or Severe Anemia or even Pancytopenia occurs, these previously dreaded hematogenic adverse effects can be easily treated. Leukopenia, Severe Anemia, and Thrombocytopenia or Pancytopenia can be normalized in a relatively short period of time by Filgrastim (Neupogen), Recombinant Human Erythropoetin (Recormon), and combination of IV Epinephrine+Methylprednisolone respectively.

**What are the renal toxicities of the SBP-6-IMNs?**

Copious fluid intake prior and after IV Cyclophosphamide prevent hemorrhagic cystitis. No other renal toxicities are found such as raise of serum creatinine over 30%.

**What are the liver toxicities of the SBP-6-IMNs?**

In the low dosages applied no liver toxicities are encountered such as raised SGPT

**What is the outcome of treatment of Lupus Nephritis by the SBP-5-IMNs in the long term?**

The first version applied in Lupus Nephritis is the SBP-5-IMNs comprising IV Cyclophosphamide + Methylprednisolone + Methotrexate and oral Mycophenolate Mofetil + Cyclosporine. When 5-Flurouracil is additional included the treatment regimen becomes SBP-6-IMNs.

Remission with oral Drugs is achieved within 7.5 months and Remission without Drug is attained within 5 years. Both can be maintained in the medium and long term by immediate suppression of early flare by the SBP-6-IMNS.

**Is Remission without Drug lasting long-term or lifetime a cure for Lupus Nephritis?**

Long term or lifetime Remission without Drug is no cure. The risk factors for flares are real and must be avoided. Early flare requires immediately suppression within 1 week of onset with the SBP-6-IMNs to maintain Remission without Drug.

**What happens when the patient dropped out during the treatment with the SBP-6-IMNs and return later for re-treatment again?**

It is very likely that the Lupus Nephritis flares in the mean time and may reach the stage of Nephrotic Syndrome. However, the patient is not Immunosuppressant-naïve anymore when retreated with the SBP-6-IMNs. Retreatment with the SBP-6-IMNs at the most achieves Remission with oral Drugs, but not Remission without Drug.

Dropout is defined of patient who does not complete the SBP-6-IMNs for any reason.

**Why are patients with Systemic Lupus Erythematosus (Lupus) still prescribed Prednisone or Prednisolone or Methylprednisolone long term or lifetime?**

Dissemination of information in international scientific medical journals takes years even decades to spread over the world to the medical professionals. What has been standard therapy takes at least one generation of medical professionals to correct. In the mean time damage has been done and the consequences endured. This website is launched to communicate the newest and latest development in the treatment of Autoimmune Diseases.

The short, medium, and long term adverse effects of Prednisone, Prednisolone or Methylprednisolone are notorious and detrimental. These agents are used as a troubleshooter and Panacea when nothing helps. However, when it is used appropriately and adequately over a relative short period of time, it is very beneficial to the patient in controlling symptoms and signs of disease.

### **ARE IV Cyclophosphamide adverse effects a risk factor for damage to the male and female fertility organs?**

In high daily dosages and high total cumulative dose applied in the treatment of cancers, IV Cyclophosphamide may be associated with infertility and malignancy. It has been accepted that a total cumulative dose of maximum 3 g, the total number of IV sessions < 30 with < 100 mg of Cyclophosphamide per IV session, and spread over period of < 1 year is a safe limit.

### **The mean cumulative and per IV session dosages, total number of IV sessions, and period of exposure to IV Cyclophosphamide and Methylprednisolone in the therapy of Lupus nephritis and Nephrotic Syndrome are identical in a 7 years observational study\*.**

Disease status	Lupus Nephritis	Nephrotic Syndrome	Lupus Nephritis	Nephrotic Syndrome
Immunosuppressant	Cyclophosphamide	Cyclophosphamide	Methylprednisolone	Methylprednisolone
Cumulative dose in mg	2025.9+925.8	2025.9+925.8	2025.9+925.8	2025.9+925.8
Per IV Session in mg	83.9+15.9	83.9+15.9	83.9+15.9	83.9+15.9
IV Session in number	21.7+7.5	21.7+7.5	27.7+7.5	21.7+7.5
Period IV therapy in weeks	41.3+9.6	41.3+9.6	41.3+9.6	41.3+9.6

In the therapy of Lupus Nephritis the total cumulative dose of Cyclophosphamide from the SBP-5-IMNs is < 3 g, IV session is < 100 mg per dose, the frequency of IV session < 30 spread over a period of < 1 year. As adverse effects are daily and cumulative dose and time-exposure dependent, it is very unlikely that the SBP-6-IMNs will induce serious reactions. The initial 5X per week daily IV session although intensive, last only 1-2 months. With regard of Cyclophosphamide the SBP-6-IMNs is a safe treatment regimen.

\* John Darmawan<sup>1</sup>, A Remy Nasution<sup>1</sup>, Dongbao Zhao<sup>2</sup>, Sun-le Chen<sup>3</sup>, Tran Thi Minh Hoa<sup>4</sup>, Syed Atiqul Haq<sup>5</sup>, Qingyu Zeng<sup>6</sup>, Fereydoun Davatchi<sup>7</sup>, Budi Liem<sup>8</sup>. Seven-years Outcome of Biopsy-proven Lupus Nephritis after Treatment with the Step-down Bridge Protocol of Intravenous and Oral Combination of 5 Immunosuppressants. Prospective Observational Analysis of Efficacies and Adverse Effects. Submitted for review and publication.

### **What about the risk of short, medium, and long term adverse effects of 5-fluorouracil used in the SBP-6-IMNs?**

5-Fluorouracil is given in daily and cumulative dosages, number of IV sessions, and period of exposure identical to Cyclophosphamide. Due to the different receptor sites for adverse effects, the patient is not collectively affected by Cyclophosphamide + 5-Fluorouracil together. Intravenous 5-Fluorouracil is as safe as IV Cyclophosphamide in the SBP-6-IMNs.

### **What about Methotrexate adverse effects?**

Methotrexate has been applied in the therapy of Rheumatoid Arthritis (RA) about 4 decades ago. It is standard and classical therapy for RA in the Western countries. Its adverse effects and safety precautions to be taken when prescribing Methotrexate is well known. Biologic Response Modifiers are always applied in combination with Methotrexate. The Biologic Response Modifiers, Infliximab (Remicade), Etanercept (Enbrel), Adalimumab (Humira), Anakinra (Kineret), and Rituximab (Mabthera) modify the response of RA to Methotrexate in the combination therapy. These are quite expensive drugs and must be applied lifetime.

### **What are the short, medium, and long term adverse effects of Mycophenolate Mofetil on the stomach?**

The daily low dosages of Mycophenolate Mofetil of 500 mg bid/tid in the maintenance of Remission with oral Drugs in Lupus Nephritis very rarely induce gastritis. The gastritis can be immediately overcome with proton pump inhibitors. Proton pump inhibitor taken before meals and the Mycophenolate Mofetil taken after meals can prevent flare of gastritis.

So far the mainstay of short, medium, and long term maintenance therapy in Remission with oral Drugs of Lupus Nephritis is Mycophenolate Mofetil (Cellcept). Cyclosporine could be more locally irritating to the stomach compared with Mycophenolate Mofetil.

**What are the most misunderstood aspects of the SBP-6-IMNs?**

The therapeutic principle of the SBP-6-IMNs is to suppress the SLAM Score from  $> 4$  to  $< 1$  and ESR from  $> 40$  mm to  $< 20$  mm/1 hour by the daily IV therapy of Cyclophosphamide + Methylprednisolone + 5-Fluorouracil and weekly Methotrexate. When the SLAM Score is  $< 1$  and ESR  $< 20$  mm, the daily oral therapy of Mycophenolate Mofetil + Cyclosporine + weekly Methotrexate consolidate the SLAM Score of  $< 1$  and ESR  $< 20$  mm for at least 2 years.

Trying to suppress SLAM Score of  $> 4$  and ESR  $> 40$  mm by the oral therapy is born to fail. The low dosages of the oral therapy within the limit of serious adverse effects are only effective when the ESR is normal and the SLAM Score  $< 1$ .

Another misunderstanding is to equate the SBP-6-IMNs with chemotherapy for cancer treatment. The IV dosages of Cyclophosphamide + Methylprednisolone + 5-Fluorouracil and weekly Methotrexate are small compared with dosages of combination of cytostatics for treatment of cancer. As adverse effects of drugs are daily and cumulative dose dependent, the SBP-6-IMNs has safe low dosages with limited time exposure (see table above).