

Postgraduate Medical Information for the Medical Practitioners

Breakthrough in the Treatment of Rheumatoid Factor Positive Rheumatoid Arthritis 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 you are diagnosed with Rheumatoid Factor Positive Rheumatoid Arthritis (RF+ RA). **What are the best treatment options immediately, in the short, medium, and long term?**

Immediately means within a week

In the short term means less than 5 years

In medium term means 5-10 years

In the long term means more than 10 years

Based on the following reasons RF+ RA is in fact an emergency situation:

1. There is continuous progression of joint destruction in patients with RF+ RA.
2. Almost 99% of the patients with RF+ RA shows joint damage after 17 years (long term).
3. Not immunosuppressant-naïve RF+ RA cannot obtain **Disease in control** and **Remission with oral Drugs**
4. Joint erosions have been healed and progression of joint destruction has been terminated.
5. Remission with oral Drugs has been achieved in those with \geq grade 2 erosions in a relative short period of time ($<$ 1 year)
6. **Remission without Drug** has been attained in those with $<$ grade 2 erosions in the short term ($<$ 5 years)

Immunosuppressant-naïve means the patient has never been exposed to any of the drugs in the Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants (SBP-6-IMNs).

Not immunosuppressant-naïve means the patient has been exposed to any of the IMNs in the SBP-6-IMNs.

Not immunosuppressant-naïve patients have been exposed to intermittent high dosages of IV Cyclophosphamide of 800-1000 mg or 1000 mg of Methylprednisolone. However, they are still immunosuppressant-naïve to IV Methotrexate + 5-Fluorouracil + Mycophenolate Mofetil and Cyclosporine and achieve improvements of ACR70.

What is improvements of ACR70?

The ACR70 is an outcome measure to record percentages of improvements up to 70% from baseline by therapy.

What is meant by Immunosuppressant-naivety with regard to the SBP-6-IMNs?

Immunosuppressant-naïve is defined when the patient has never 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.

Disease in Control of RF+ RA is defined when the signs, symptoms, and function of the body organs, and laboratory changes are normalized by treatment with the SBP-6-IMNs. Disease in Control is achieved in 2-4 months.

Remission with oral Drugs is defined when the IV therapy of the SBP-6-IMNs is tapered off during Disease in Control and similar status is maintained by oral therapy. Remission with oral Drugs is acquired in 5.5-7.5 months and this must be consolidated for at least 2 years.

Remission without Drug is defined when the oral therapy of the SBP-6-IMNS is tapered off over a period of 1 year with similar status retained as in Remission with oral Drugs. Remission without Drug is achieved in 3.5 – 4.5 years and must be maintained long term or lifetime by immediate suppression of early flare by the SBP-6-IMNs.

Flare is defined when arthritis recurs in ≥ 1 joint with abnormal levels of ESR and CRP.

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

All early flares during Disease in Control or Remission under IV and Oral Therapy, Remission with oral Drugs, the 1 year period during tapering of oral Drugs, and Remission without Drug, must be immediately suppressed by re-institution of the IV therapy.

Contemporary the best treatment regimen for RF+ RA is the Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants (SBP-6-IMNs) for RF+ RA
RF+ RA must be controlled (Disease in Control) as soon as is possible before \geq grade 2 erosions are seen on X-ray films.

The schedules of the SBP-6-IMNs application in patients with RF+ RA

1. Initially, intensive daily application of the SBP-6-IMNs. This is limited to 5X weekly with duration of treatment over a period of 1-2 months.
2. Declining frequency of intravenous therapy to 3, 2, and once weekly in accordance with the declining Erythrocyte Sedimentation Rate (ESR) levels to < 40 mm, < 30 mm, and < 25 mm respectively over a period of 1-2 months
3. After ESR and the titer of CRP are suppressed to < 20 mm (men < 10 mm) per 1 hour and < 3 mg%, Disease in Control is achieved. During the period of 3.5 months of Disease in Control, the IV therapy is tapered off fortnightly, once monthly, bimonthly and terminated.
4. After the IV therapy is terminated, Remission must be maintained with oral drugs for at least 2 years. This condition is called Remission with oral Drugs.
5. During the 3rd year Oral Therapy should be tapered off if no flare occurs
6. After the 3.5-4.5 year without drug and without flare, Remission without Drug is achieved

Early flare during Disease in Control, Remission with oral Drugs, tapering off drugs, the period of 1 year without drug and flare, must be immediately suppressed by the SBP-6-IMNs.

How long does it takes to obtain Disease in Control in patients with RF+ RA?

Mean 2-4 months

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

Mean 5.5-7.5 months

How long does it takes to acquire Remission without Drugs?

Mean 5.5-7.5 months plus 3 years or 41.5-43.5 months

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

Only Immunosuppressant-naïve patients with RF+ RA with < grade 2 erosion 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 1st week of onset by the SBP-6-IMNs.

What are the best treatment options in the medium term of 5-10 Years?

Those patients who have been exposed to Immunosuppressants (not Immunosuppressant- naïve) with \geq grade 2 erosion do not acquire Remission with oral Drugs. These patients achieve improvements of ACR70.

Those patients who are Immunosuppressant-naïve but with \geq grade 2 erosions attain Remission with oral Drugs

Remission with oral Drugs is sustained through medium term by immediate suppression of early flare with the SBP-6-IMNs.

Remission without Drug is sustained through medium term if early flares are immediately suppressed by the SBP-6-IMNs.

What is the best treatment options in the long-term?

When required Remission with oral Drugs is sustained through long-term or lifetime by immediate suppression of early flare with 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 are the outcome of the treatment of RF+ RA with the SBP-6-IMNs**In the short term**

Disease in Control or Remission under IV and Oral Therapy

Remission with oral Drugs

Remission without Drug

In the medium term

Maintenance of Remission with oral Drugs

Sustaining Remission without Drug by prevention of flares with the SBP-6-IMNs

In the long-term

Maintenance of Remission with oral Drugs

Sustaining Remission without Drug by prevention of 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. These symptoms and signs are easily prevented by preceding IV infusion with Granisetron (Kytril), H₂ Antagonists and/or Proton Pump Inhibitor, antiemetic and spasmolytic.

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 Erythropoietin (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.

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

In the low dosages applied no liver toxicities are encountered

The outcome of 271 patients with RF+ RA treated with the SBP-5-IMNs in a 7 years observational study.

51.3% of the patients with Immunosuppressant-naïve but \geq grade 2 erosions achieve Remission with oral Drugs and remain so in the medium term.

40.2% of the patients with Immunosuppressant-naïve and $<$ grade 2 erosions acquires Remission without Drug with flares prevented in the medium term.

1.5% or 4 patients who are not Immunosuppressant-naïve but with \geq grade 2 erosions cannot achieve Disease in Control and Remission with oral Drugs. These 4 patients obtain improvements of ACR70.

Is Remission without Drug lasting long-term or lifetime a cure for RF+ RA?

Long term or lifetime Remission without Drug is no cure. The risk factors that can induce flares are real such as physical and/or mental trauma. Flare requires immediately suppression by 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 RF+ RA flares in the mean time into a more severe disease. However, the patient is not Immunosuppressant-naïve anymore when retreated with the SBP-6-IMNs. At the most retreatment with the SBP-6-IMNs achieve improvements of ACR70. Remission without Drug is out of the question and Remission with oral Drugs is more difficult to achieve.

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

It is evident that oral corticosteroids are potentially damaging to the organs in patients with Systemic Lupus Erythematosus after 15 years*.

*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;330(9):1955-1999.

These organ damages in Lupus Nephritis would occur in any other autoimmune diseases such as in RF+ RA.

Why are some patients with RF+ RA still prescribed Prednisone or Prednisolone or Methylprednisolone for 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 RF+ RA.

The short, medium, and long term adverse effects of Prednisone, Prednisolone or Methylprednisolone are notorious and detrimental to the health of the patient. These agents are used as a trouble shooter 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.

Is 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. Less than 100 mg of Cyclophosphamide per IV session, total cumulative dose of maximum 3 g, total number of IV sessions $<$ 30 spread over period of $<$ 1 year are not associated with gonadal toxicities.

Per IV session and cumulative dosages, total number of IV sessions, and period of exposure to IV Cyclophosphamide and Methylprednisolone in the therapy of RF+ RA are identical in a 7 years observational study*.

| Immunosuppressant | Cyclophosphamide | Methylprednisolone |
|----------------------------|------------------|--------------------|
| Cumulative dose in mg | 2025.9±925.8 | 2025.9±925.8 |
| Per IV Session in mg | 83.9±15.9 | 83.9±15.9 |
| IV Session in number | 21.7±7.5 | 27.7±7.5 |
| Period IV therapy in weeks | 41.3±9.6 | 41.3±9.6 |

As adverse effects are IV 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 Darmawan¹, A Remy Nasution¹, Dongbao Zhao², Sun-le Chen³, Tran Thi Minh Hoa⁴, Syed Atiqul Haq⁵, Qingyu Zeng⁶, Fereydoun Davatchi⁷, Budi Liem⁸. 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 IV 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 are wellknown. Biologic Response Modifiers are always applied in combination with Methotrexate in the treatment of RA. 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 is 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 RF+ RA very rarely induce gastritis. The gastritis can be immediately overcome with proton pump inhibitors. Flare of gastritis can be prevented by proton pump inhibitor taken before meals and the Mycophenolate Mofetil after meals.

So far the mainstay of short, medium, and long term maintenance therapy in Remission with oral Drugs of RF+ RA is Mycophenolate Mofetil (Cellcept). Cyclosporine could be more locally irritating to the stomach compared with Mycophenolate Mofetil. Most patients with RF+ RA are not immunosuppressant-naïve to Methotrexate anymore.

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

The therapeutic principle of the SBP-6-IMNs is to suppress the Endpoints Scores to normal 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 endpoint scores and ESR are normalized, the daily oral therapy of Mycophenolate Mofetil + Cyclosporine + weekly Methotrexate consolidate these endpoint scores and normal ESR for at least 2 years.

Trying to suppress abnormal endpoint scores 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 is only effective when the ESR and the endpoint scores are normalized.

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 is minuscule 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).