

Postgraduate Medical Information for Rheumatologists

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

Introduction

The Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants (SBP-6-IMNs) is the breakthrough in the treatment of Rheumatoid Factor Positive Rheumatoid Arthritis (RF+ RA). This treatment regimen is a novel approach to the therapy of almost all Autoimmune Diseases. The SBP-5-IMNs has been applied for over more than 10 years in the treatment of RF+ RA guided by the ESR and CRP[1,2,3]. The following reasons justified the early application of the SBP-6-IMNs in early RF+ RA. The SBP-6-IMNs comprises Intravenous (IV), Oral, and local (intraarticular & intralesional) therapy.

RF+ RA is considered an emergency situation when the diagnose is established because of the following facts:

1. There is continuous progression of radiological destruction in Rheumatoid Arthritis (RF+ RA)[4].
2. Almost 99% of the patients with RF+ RA shows erosions after 17 years[5].

Radiological remission of RA has occurred with healing and termination of the progression of joint erosions [6].

This is clinically confirmed by:

1. patients with Larsen grade < 2 erosions achieve Remission without Drug
2. patients with ≥ 2 erosions achieve Remission with oral Drugs

Healing of erosions is achieved with termination of the progression of radiological joint deterioration and new erosion is prevented, whatever the grades of erosions and diseases duration[3]

Prognosis

The most important prognostic factor is the treatment and grades of erosion independent of disease duration. Disease activity and disease duration dependent grades of erosions determine outcome of RF+ RA. Single drug therapy with 1 DMARD or Immunosuppressant is not or less effective in moderate or severe RA[7].

Based on the abovementioned reasons the application of the Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants (SBP-6-IMNs) in RF+ RA is justified. However, only immunosuppressants-naïve RF+ RA with < grade 2 erosions can achieve Disease in Control (DiC), subsequent Remission with oral Drugs (RworalDs), and ultimately, Remission without Drug (RwD).

The therapeutic principle is to achieve Disease in Control or induction of Remission at the shortest period of time by the SBP-6-IMNs without serious adverse effects, before \geq grade 2 erosions (Larsen) appear.

Disease in Control

Disease in Control ([identical to Remission under Intravenous and Oral Therapy](#)) is defined [3] when:

- signs and symptoms are:

1. mean swollen and tender joint count are < 1
2. normal CRP (< 3 mg%)
3. mean ESR < 25 mm/1 hour (men < 15 mm) Westergren
4. mean Patient Global Assessment ≥ 4 (1-5)
5. mean Visual Analog pain Scale ≤ 10 (0-100)

- functional impairment

1. mean ARA Functional Class < 2 (0-4)

- radiological progression of the disease

1. mean Rau modified Larsen Index and Erosive Joint Count zero or not significantly worse compared with baseline.
2. Grade < 2 erosions healed (Larsen Index and Erosive Joint Count zero)
3. **New erosion prevented.**

Remission with oral Drugs

After 2 years consolidation of Rworalds with MMF + CyS + MTX/wk, attempts should be made to taper off drugs. Tapering of oral drugs requires at least 1 year and, Rwd is achieved. If 2 flares appear during repeated tapering of drugs, Rworalds should be maintained medium to long-term.

Remission with oral Drugs is defined when the status of DiC is sustained for at least 2 years by the Oral therapy after termination of IV therapy[3].

Remission without Drug

Remission without Drug is defined when identical status as Rworalds is maintained after Oral therapy is tapered off over a period of 1 year [3].

The definitions of DiC, Rworalds, and Rwd are more exacting than the improvements of ACR20, ACR50, and ACR70.

Flare

Flare is defined when arthritis re-appeared in ≥ 1 joints with abnormal titer of CRP and ESR[3]. Early flare (within 1 week onset) during DiC, Rworalds, and in Rwd must be immediately suppressed by reinstatement of the SBP-6-IMNs. Only 1-2 weeks is required to suppress early flare. Full-blown flare requires the total treatment schedules of the SBP-6-IMNs.

When to apply the SBP-6-IMNs?

When RF+ RA is diagnosed with ESR of > 40 mm/1 hour Westergren (men > 30 mm) the SBP-6-IMNs is empirically applied to obtain DiC or to induce Remission as soon as is possible before \geq grade 2 erosions is identified in the X-ray films.

Contra-indications

The contra-indications for the application of single or combination drug therapy of RF+ RA with immunosuppressants such as CyC (Cyclophosphamide), MPS (Methylprednisolone), 5FU (5-Fluorouracil), MTX (Methotrexate), MMF (Mycophenolate Mofetil), and CyS (Cyclosporine) are obvious. The inserted leaflets in the package of each individual immunosuppressant from the manufacturers are self-explanatory.

Exclusion

Not IMN-naïve RF+ RA is excluded for treatment with the SBP-6-IMNs. The patient must be IMN-naïve to IV CYC+MPS+5FU+MTX for achievement of DiC and Rworalds. In not IMN-naïve patients treatment with SBP-6-IMNs obtain improvement of ACR70.

Methods

The standard daily 5X weekly intravenous CyC + MPS + 5FU + weekly MTX without oral corticosteroid is applied. Oral corticosteroid at presentation is directly terminated when the IV therapy is initiated[3]. The IV MTX/wk is preferred because oral one has lower bioavailability[8]. The maximum number of daily intravenous sessions is limited to 5 times per week to avoid high weekly cumulative dose-dependent adverse effects.

The IV Dosages are

daily

1. CyC[9] 25-100 mg per session
2. MPS[9] 25-125 mg per session
2. MTX[10] 5-15 mg per session
2. 5FU 25-100 mg per session)[11,12]

Patients with Diabetes Mellitus (DM) and/or a history of melena and/or hematemesis are not given IV MPS to avoid exacerbation of DM and recurrence of melena or hematemesis. The IV therapy consists of only CYC + 5FU + MTX.

Intravenous MPS is in fact not absolutely required to achieve DiC and Rworalds. It is relatively required to taper off and achieve DiC in patients still on oral corticosteroids at presentation. Nevertheless, the combination of IV CyC + 5FU + MPS + MTX/wk achieves faster DiC with reduction of the number of IV sessions. The IV CyC + 5FU + MPS + MTX/wk tides over the dependency on corticosteroids at presentation when it is terminated on initiation of the SBP-6-IMNs.

Tapering Off IV Therapy

After ESR dropped to < 40, < 30, and < 25 mm/hour (men < 30, < 20, and < 15 mm), the IV session is tapered to 3X, 2X, and 1X weekly respectively. When ESR is < 25 (women) or < 15 mm (men) RF+ RA has attained DiC. The IV session is then tapered to once fortnightly (in conjunction with switching IV MTX/wk to oral MTX/wk) 4-weekly, 8-weekly and then terminated to Rworalds.

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 derivatives of the broad spectrum Cephalosporines or its derivatives can be given to lower resistant CRP level. The Quinolones interact with immunosuppressants and should be avoided.

Oral Therapy

Oral therapy comprises:

1. Mycophenolate Mofetil (MMF)* 500 mg bid-tid[13] +
2. Methotrexate** 5-15 mg per week when the IV MTX/wk is terminated[14] +
3. Cyclosporine (CyS)* 50 mg bid-tid[15].

*MMF and CyS have been prescribed for > 10 years in transplant patients. Its efficacy and safety is evident in the lifetime prevention of organ rejection in transplantation.

**MTX has been prescribed for RA for > 30 years. With regular and adequate monitoring of adverse effects and safe application, these oral immunosuppressants should be made long-term available for maintenance of Rworalds in patients with RF+ RA.

Oral 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 during the period of in 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 and CRP are normalized and stabilized with the IV therapy terminated.

Trying to suppress the autoimmune inflammation of RF+ RA with ESR of more than 40 mm/1 hour (> 30 mm/1 hour in men) by low dosages of Oral therapy is inclined to fail, at least at the low oral dosages of CyS + MMF + MTX/wk applied within the limit without adverse effects.

Oral MPS[16] and CyC[17] are not prescribed for reasons of more severe and more frequent adverse effects compared with intravenous administration. The IV therapy achieves fast, 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 achieving Rwd in immunosuppressant-naïve < grade erosions RF+ RA are:

- 1-2 months daily IV therapy (limited to 5 sessions per week to avoid weekly cumulative dose-dependent adverse effects)
- 1-2 months declining frequency of IV sessions to DiC

3.5 months DiC for 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.

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 sessions last only mean 1-2 months, except in long-standing disease. As Rworalds is attained after 5-10 months by IV therapy, the total cumulative dose and period of exposure to IV therapy is limited. This has prevented serious adverse effects, except mild gastrointestinal (GI) ones[3].

Prevention of gastrointestinal adverse effects

Preceding the IV therapy with intravenous Granisetron (Kytril), H₂ Antagonists and/or Proton Pump Inhibitor, antiemetic and spasmolytic has minimized the GI adverse effects. Mild GI adverse effects were 55.5% when the first version of this protocol was applied in the initial open label observational study[3], but only 25.0% when the improved second version of the protocol was applied[18]. This was achieved by intensification of prevention of gastrointestinal adverse effects such as anorexia, nausea, vomiting, and diarrheas. H₂ 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 IMNs are suppressed and prevented by Granisetron. Preceding IV drips of spasmolytics prevents diarrheas.

Monitoring of hematological adverse effects

Monitoring of hematological adverse effects of the SBP-6-IMNs by standard laboratory procedures 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[19] + IV MPS

When Pancytopenia occurs, the SBP-6-IMNs 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 combined with the SBP-6-IMNs without transfusion of leucocytes, thrombocytes, and blood. The reasons are that transfused thrombocytes, leucocytes, and erythrocytes are destroyed within 1 week by the antibodies.

Prevention 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) and discomfort of the patients[19]. 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.

Intraarticular and Intralesional Injections

Intraarticular injections for persistent chronic arthritis and intralesional injections for enthesitis, bursitis, tendonitis, and/or Fibromyalgia Syndrome (here is Fibromyalgia a complication of rheumatoid arthritis) 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%.

Co-morbidity

Co-morbidity or associated conditions such as Hypertension, Diabetes Mellitus, Artherosclerosis, Neuropathy, Osteoporosis, etc., must be treated simultaneously with the RF+ RA. Osteoporosis can be due to corticosteroids abuse or menopause, or advanced age (> 60-70 years), or immobility or any one, two, three or all four factors combined. Intravenous Zoledronic Acid[20] 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 SBP-6-IMNS for any reason. Dropouts never achieve DiC, Rworalds or Rwd, but nevertheless, considerable improvements still occur in these irregular treated patients[21].

Outcome Measures

The choice of Outcome Measures is left to the discretion of the main investigator. The modified HAQ and ACR70 can be additionally included in the outcome measures.

The SBP-6-IMNs for the Therapy of RF+ RA is applicable to almost all other Autoimmune Disorders

Almost all the cases with autoimmune inflammation such as IMN-naïve Biopsy-proven Lupus Nephritis[21] and Nephrotic Syndrome, NSAID-Refractory Reactive Arthritis, NSAID-Refractory Ankylosing Spondylitis[22], Psoriatic Arthritis, Systemic Progressive Scleroderma, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Alzheimer's Disease, etc, can be brought into DiC and long-term Rworalds. In Systemic Progressive Scleroderma it takes at least 2 year before the skin texture is normalized by Oral therapy after termination of IV therapy.

Summary

High level of ESR¹ and CRP² indicates activity and severity of the disease and correlate with outcome of RF+ RA. Suppression of ESR and CRP to normal by the "SBP-6-IMNs in the Therapy of RF+ RA," inactivate the disease clinically and radiologically[3]. Intravenous therapy serves to normalize the ESR and CRP in a relatively short period of time and achieve DiC and Rworalds. The Oral therapy serves to maintain the normal level of ESR and CRP achieved by the IV therapy. Gastrointestinal adverse effects are common, but the dreaded hematological, renal, and liver ones are not encountered. Hematological toxicities are easily normalized by Filgrastim, Recombinant Human Erythropoietin, and diluted solution of Epinephrine plus MPS. 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 has been obtained and in early RF+ RA with Larsen Erosion Grade of < 2, Rwd has been achieved[18].

Acknowledgements

The comments and suggestions from Professors Hans A Valkenburg, former Head, Department of Epidemiology, Erasmus University Rotterdam, Rotterdam, The Netherlands, and Johannes J Rasker, former Head, Departments Rheumatology, Medisch Spectrum Twente and Communication Studies University Twente, Enschede, The Netherlands, are very much appreciated.

References.

1. Sox H, Liang M: The erythrocyte sedimentation rate. Guidelines for rationale use. *Ann Intern Med* 1986;104:515-23.
2. Devlin J, Gough A, Huissoon A, Perkins P, Holder R, Reece R, Arthur V, Emery P. The Acute Phase and Function in Early Rheumatoid Arthritis. C-Reactive Protein Levels Correlate with Outcome. *J Rheumatol* 1997;24:9-13
3. John Darmawan, Johannes J. Rasker, and Hendri Nuralim. Ten years radiographic outcome of rheumatoid factor positive rheumatoid arthritis patients, treated with aggressive immunosuppressive combination therapy. *J Rheumatol* 2004;31 suppl 69:66-69.
4. Kaarela K, Kautiainen H, Continuous Progression of Radiological Destruction in Seropositive Rheumatoid Arthritis. *J Rheumatol* 1997;24:1285-1287.
5. Kaarela K, Lukkainen R, Koskimies S. How often is seropositive rheumatoid arthritis an erosive disease? A 17-year followup study. *J Rheumatol* 1993;20:1670-1673.
6. Jantti J, Kaarela K, Kautiainen H, Isomaki H, Aho K. Radiographic remission in seropositive rheumatoid arthritis. A 20-year follow-up study. *Clin Exp Rheumatol*. 2001;19:573-6.
7. Jantti JK, Kaarela K, Luukkainen RK, Kautiainen HJ. Prediction of 20-year outcome at onset of seropositive rheumatoid arthritis. *Clin Exp Rheumatol*. 2000;3:387-90.
8. John Darmawan (2001). Therapeutic Principles - Treatment Rheumatoid Arthritis. Disorders of Connective Tissue, Bone and Joints. In: Chris J van Boxtel, Budiono Santoso, I Ralph Edwards (eds) Drug Benefits and Risks – International Text Book of Clinical Pharmacology, pp 571-572;574-576 John Wiley & Sons, LTD, Chichester.
9. Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. *Am J Med* 1984;76:377-384.
10. Shiroky JB, Neville C, Skelton JD. High dose intravenous methotrexate for refractory rheumatoid arthritis. *J Rheumatol*. 1992 Feb;19(2):247-51.
11. Jensen AO, Mejer J. Remission of methotrexate-resistant rheumatoid arthritis after receiving 5-fluorouracil for colon cancer. *J Intern Med*. 2003;254:395-6.
12. Bunch TW, Erlichman C, Luthra HS, Matteson EL. An open-label, phase I/II study of 5-fluorouracil plus leucovorin in the treatment of rheumatoid arthritis. *J Rheumatol*.2002;29:1109-10.
13. Goldblum R. Therapy of rheumatoid arthritis with mycophenolate mofetil. *Clin Exp Rheumatol* 1993;11 Suppl 8:S117-119.
14. Kremer JM. Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate. Followup after a mean of 13.3 years. *Arthritis Rheum* 1997;40:984-985.
15. Pasero G, Priolo F, Marubini E et al: Slow progression of joint damage in early rheumatoid arthritis treated with cyclosporine A. *Arthritis Rheum* 1996;39:1006-15.
16. M Petri, Zonana-Nacach, S Barr, L Magder. Damage in systemic lupus erythematosus is dependent on dose and mode of delivery of corticosteroid. *Arthritis Rheum* 1999;42:(suppl9)S97.
17. Haubitz M, Schellong S, Gobel U et al. Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum* 1998;41:1835-44.
18. John Darmawan, Johannes J Rasker, A Remy Nasution, Syed Atiqul Haq, Qingyu Zeng, Fereydoun Davatchi, Tran Thi Minh Hoa, Dongbao Zhao, Budi Liem. Outcome Of Rheumatoid Factor Positive Rheumatoid Arthritis After 7-years Immunosuppressiv Combination Therapy. (Submitted for review and publication.
19. Smith D, Riel J, Tilles I, Kino R, Lis J, Hoffman JR. Intravenous epinephrine in life-threatening asthma. *Ann Emerg Med*. 2003 May;41(5):706-11.
20. Doggrell SA. Zoledronate once-yearly increases bone mineral density—implications for osteoporosis. *Expert Opin Pharmacother*. 2002 Jul;3(7):1007-9.
21. John Darmawan, A Remy Nasution, Dongbao Zhao, Sun-le Chen, Tran Thi Minh Hoa, Syed Atiqul Haq, Qingyu Zeng, Fereydoun Davatchi, Budi Liem. Outcome of Biopsy Proven Lupus Nephritis after 7-years Immunosuppressive Combination Therapy - A Prospective Observational Inception Cohort Analysis of Efficacy.
22. John Darmawan, A Remy Nasution, Dongbao Zhao, Sun-le Chen, Tran Thi Minh Hoa, Syed Atiqul Haq, Qingyu Zeng, Fereydoun Davatchi, Budi Liem. Outcome of NSAIDs-Refractory Ankylosing Spondylitis After 6-years Immunosuppressive Combination Therapy - A Prospective Observational Inception Cohort Analysis of Efficacy. (Finalizing the manuscript by the co-authors).