



John Darmawan, MD, PhD
Member, WHO Expert Advisory Panel on the Rheumatic Diseases, Geneva, Switzerland
1992-1996; 1996-2000; 2000-2003; 2003-2007

Jalan Seroja Dalam 7, Semarang 50136, Indonesia
Tel. 62 24 8316 496, 62 24 8447 345, Fax.62 24 8310 028
Email: jd131035@hotmail.com

John Bridge Therapy or Step-down Bridge Combination of Five Immunosuppressants (SBC-5-IMNs) in the Treatment of Refractory Autoimmune Diseases

Refractory Autoimmune Diseases are: RA, AS, PsA, ReA, Lupus Nephritis, Nephrotic Syndrome, etc, which are refractory to single or combination drugs therapy of NSAIDs, corticosteroids, Sulfasalazine Hydroxychloroquine, and Methotrexate.

Principles:

1. Suppression of Cytokines dependent pathway [1] of the autoimmune inflammation is by intravenous low and safe dosages of combination of 5X weekly daily Cyclophosphamide + 5-Fluorouracil + weekly Methotrexate. (This combination also affects the cytokines independent pathway of activated synovial fibroblasts).

2. Suppression of Cytokines independent pathway (activated Synovial Fibroblasts) [2] is by weekly polyarticular injections and infiltrations (the latter in Enthesitis and Fibromyalgia) [3,4] of the combination of Lignocain + Dexamethasone+ Triamcynolone (in minute amounts to avoid systemic adverse effects of corticosteroids). Weekly polyarticular injections also affects the cytokines dependent pathway in the synovium of the joints.

The rationale of this mixture is instant anesthesia up to 4 hours by Lignocain; efficacy of Dexamethasone commences after 4 hours up to 4 days; efficacy of Triamcynolone Acetonide is effective after 4 days up to < 6 days. Efficacy of polyarticular injection lasts at least for 10 up to 14 days unless the joint becomes refractory to local corticosteroids.

Administration of weekly polyarticular corticosteroids is required over a relative short period of less than 2 months with minute amount of the mixture, before pain is abolished. No oral corticosteroids are administered by the John Bridge Therapy. Existing oral

corticosteroids are replaced by equivalent dosages of intravenous ones when intravenous sessions are initiated.

3. Maintenance of Remission: when ESR of < 20 mm (male < 10 mm) is achieved: oral Mycophenolate Mofetil + Cyclosporine in low and safe dosages (these dosages are not at all effective in autoimmune diseases with ESR > 40 mm, but high intolerable oral dosages may be effective)) are administered for at least 2 years. When intravenous Methotrexate is tapered off, it can be replaced with an equivalent oral dose for additional efficacy without additional adverse effects [5].

The principles of intravenous administration is: it generates maximum, fast, and long lasting efficacy with minimum adverse effects compared with oral therapy which generate minimum, slow, short lasting efficacy with maximum adverse effects.

Maximum efficacy is achieved if the patients are immuno-naïve to intravenous Cyclophosphamide, 5-Fluorouracil, and Methotrexate. Patient may be not immuno-naïve to oral Methotrexate, but intravenous Methotrexate is still effective.

John Bridge Therapy is only applied in autoimmune diseases refractory to single or combination drugs therapy of oral NSAIDs, Sulfasalazine, Methylprednisolone, Hydroxychloroquine, and Methotrexate.

John Bridge Therapy and anti TNF-a

Theoretically, anti TNF-a would block only the cytokines dependent pathway. That is why ACR 20, 50, and 70 and ASAS 20, 50, and 70 responders are < 70%, < 50%, and < 20% respectively.

1. Anti TNF-a combined with weekly low dosage of Methotrexate is effective in the treatment of several refractory autoimmune diseases such as RA, AS, PsA, etc.
2. Patients on immunosuppressants tend to have less frequency of autoantibody formation to anti TNF-a and infusion related reactions. The combination of John Bridge Therapy with anti TNF-a also far has not been a problem clinically, save for the prohibitive costs of Infliximab and Enbrel.
3. When RA, AS, and PsA are refractory to John Bridge Therapy, BRM is additionally indicated.

Refractory Ankylosing Spondylitis

Introduction

COX1 and COX2 Non Steroidal Anti-Inflammatory Drugs (NSAIDs) [6] and physical therapy have been the standard for treatment of Ankylosing Spondylitis (AS) [7]. Sulfasalazine shows only some variable beneficial effect in the peripheral joints in the short term [5]. NSAIDs neither stop nor slow the progression of AS in NSAID-refractory

AS, but have been associated with notorious gastrointestinal [9], renal [10], and liver [11] toxicity with a high dropout rate. NSAIDs also, have been associated with cardiovascular toxicities [12,13]

Open label studies of Methotrexate (MTX)[4,15], pulse intravenous (IV) Methylprednisolone (MPS)[16] and Cyclophosphamide (CyC)[17], oral Cyclosporine (CyS)[18] and Mycophenolate Mofetil (MMF)[19] in single drug therapy show varying efficacy in the treatment of AS. One Immunosuppressants (IMN) will not suppress all mediators of autoimmune inflammation as reflected in the various types of cytokines and autoantibodies of the inflammatory cascade [20]. Therefore, combination therapy may be required when treating AS with MTX [12,21].

The natural history of AS shows continuous linear progression of radiological changes and over any period of 10 years progressed to 35%. Radiological cervical spine progression is a function of disease duration, severity of lumbar and hip involvement, and a history of iritis [22].

Biologic Response Modifiers

The small minority who achieves ASAS70 (around 20%) with the Biologic Response Modifiers (BRMs) [23,24,25,26,27,28,29] may be due to only TNF-*alfa* being antagonized. This leaves all the cytokines and all autoantibodies uninhibited to continue the inflammation. Consequently: no normal level of ESR [30] and CRP [30,31] are obtained

The annual expenses for therapy of RA with the BRMs combined with Methotrexate are \$15,000.00 to \$25,000.00 [32]. This is unaffordable to the majority to the population of the Third World without health insurance and social security. The third world per capita income is less than US\$1,000.00 - 2,000.00. The cost of BRMs for therapy of patients with Nr-AS is similar to treatment of RA.

The frequency of long-term administration of BRMs in NR-AS is similar to RA consequently annual drug expenses are equivalent. A less expensive alternative therapy must be derived from existing IMNs in the Third World that shows efficacy in Nr-AS. When Nr-AS is indicated for treatment with the BRMs, but costs are prohibitive then the SBC-5-IMNs is an effective, safe, and significantly less expensive alternative in the Third World.

The BMRs such as Infliximab (Remicade), Etanercept (Enbrel), Adalimumab (Humira), and Anakinra (Kineret) which are all TNF-*alfa* antagonist, applied in long-standing RA (> 10 years disease duration) may rarely induce positive lupus serologies, proliferative or membranous or crescentic glomerulonephritis with or without Nephrotic Syndrome. The glomerulonephritis may develop via the induction of rheumatoid arthritis-related nephropathy or de novo autoimmune disorders because of Anti-TNF-*alfa* therapy. [33] Anti-TNF-*alfa* therapy should not be applied in patients with Lupus. When biopsy-proven LN Class III, IV, and V appear during the application of the TNF-*alfa* antagonists, the BRMs must be immediately withdrawn and the SBC-5-IMNs prescribed.

Response Modifiers-induced lupus serologies and LN will be eradicated permanently by the SBC-5-IMNs. For treatment of SLE or only positive lupus serologies induced by BRMs, oral IMN is adequate.

In developed countries with health insurance and social securities, it is hardly possible to get Nr-AS in remission. In developing countries without health insurance and

social securities talking about remission may be inappropriate. Even in the First and Second World, Health Insurance does not pay the BRMs for all patients with Nr-AS. Only very few patients with Nr-AS in the Third World can afford the long-term or lifetime BRMs without or with Methotrexate.

Step-down Bridge Combination of Five Immunosuppressants or John Bridge Therapy

Immunosuppressants

One IMN will not suppress the various aspects of autoimmune inflammation, as reflected in the TNF-*alfa* and different types of cytokines and all autoantibodies provoking the inflammatory process. Therefore, combination of IMNs is justified in the treatment of Nr-AS. The SBC-5-IMNs in the Therapy of refractory NR-AS is a combination of generic IMNs. The combination of DMARDs comprising oral MPS, Hydroxychloroquine, Sulfasalazine, Azathioprine, COX1 and COX2 NSAIDs, are less effective compared with the IV therapy of the SBC-5-IMNs.

Using IV generic Cyclophosphamide (CyC), Methylprednisolone (MPS)/5-Fluorouracil (5FU), Methotrexate (MTX), and generic oral Mycophenolate Mofetil (MMF) and Cyclosporine (CyS), the estimated first-year costs of treatment with the SBC-5-IMNs is US\$1500.00. The second year is around US\$1,000 and the third year is US\$500.00 for oral drugs. In Remission without Drug (RwD) there are no drug expenses after 3 years. Those in Remission with oral Drugs (RworalDs) require long-term maintenance with MMF, which cost less than US5.00 annually. This is obviously less expensive than the annual treatment costs with BRMs of US\$15,000.00 to US\$25,000.00 for long-term or lifetime. Indeed, the SBC-5-IMNs is a less expensive alternative in patients with autoimmune diseases in the Third World with over 4 billion population. Those patients with Nr-AS who cannot afford BRMs the Step-down Bridge Combination of 5 Immunosuppressants (SBC-5-IMNs) is the appropriate therapy.

Based on the abovementioned considerations, John Darmawan, MD, PhD, through trials and errors over more than 5 years has concocted the Step-down Bridge Combination of Five Immunosuppressants (SBC-5-IMNs) for therapy of Nr-AS. The SBC-5-IMNs is a three-steps treatment comprising IV CyC+5FU+MTX and weekly polyarticular injections and infiltrations of the combination of Lignocain + Dexamethasone + Triamcynolone in minute amounts to avoid corticosteroids adverse effects. When ESR has achieved a level of ≤ 20 mm, the step-down oral MMF is initiated.

Immuno-pathogenesis

It may be theoretically speculated that efficacy of the SBC-5-IMNs is due to suppression of activated T-cells, B-cells, and Macrophages with inhibition of the secretion of TNF-*alfa*, all cytokines and all autoantibodies by the IV Cyclophosphamide+5-Fluorouracil+Methotrexate (CyC+5FU+MTX). Suppression of the secretion of the TNF-*alfa*, all cytokines and autoantibodies may explain achievement of Primary Endpoint of ASAS 20, and Secondary Endpoint of ASAS 40, ASAS 70, ESR $\leq 20/10$ mm, clinical remission, and radiological remission in the majority of patients with Nr-AS.

Indications for Treatment of Nr-AS with the IV Sessions of the SBC-5-IMNs.

1. Pain (0-10) ≥ 4
2. BASDAI [34] ≥ 4
3. Erythrocyte Sedimentation Rate (ESR) of ≥ 40 mm (men ≥ 30 mm),
4. Swollen Joint Count ≥ 1
5. Tender Joint Count is ≥ 1
6. Indicated for treatment with 1 of the BRMs, but patient cannot afford the costs

The NR-AS patients with erosion BASRI < grade 2 or BASRI \geq grade 2, [35,36] with:

1. Pain is $\geq 2 - < 4$
2. BASDAI $\geq 2 - < 4$
3. ESR is $\geq 20 - < 40$ mm
4. Swollen joint count ≥ 1
5. Tender joint count ≥ 1

Radiological joint erosions are not always progressive as a small percentage of Nr-AS patients may enjoy spontaneous Remission. When the erosions are progressive, these patients should be treated with the SBC-5-IMNs. Therefore, these exceptional patients must have regular radiological follow up every 2 years.

Clinical Remission of Nr-AS is defined when:

1. Pain is zero
2. Clinical BAS Indexes < 1
3. ESR is ≤ 10 mm (men ≤ 5)
4. Swollen Joint Count is zero
5. Tender Joint Count is zero

The BAS indexes are: BASFI [37], BASG [38], and BASMI [39]

Radiological Remission of Nr-AS is defined when:

1. BASRI < 2 : healing of erosion or normalization of the axial and peripheral joints
2. BASRI ≥ 2 : termination of progression of baseline calcification with erosion healed, new erosion prevented and in status quo are baseline:

spine: sclerosis, syndesmophytes; squared and fused vertebrae, and kyphosis.

hip joint: sclerosis, osteophytes; loss of joint space; bone on bone apposition;

protrusion-acetabuli; and bone deformity.

However, the BASRI-spine and BASRI-hip prove to be insensitive to change in the Short and Medium Term (manuscript submitted to The Journal of Rheumatology). The Members of EULAR ASAS (Ankylosing Spondylitis Assessment) therefore have commenced Inception Cohort Studies of AS with Magnetic Resonance Imaging (MRI) as the tool for diagnosis and assessment of change in drug trials.

However, the individual variations of normal ESR can be baffling as in a few patients it can be normal or even < 10 mm with mild to moderate disease activity. This is in particular true in chronic longstanding AS. After 1 week of IV therapy the ESR may rise

to abnormal level before dropping to normal again or may even drop to ≤ 10 . Long standing (> 15 - 20 years) high ESR (> 100 mm) may not decline after application of the SBG-5-IMNs if the patients are IMN non-naïve. On the other hand disease duration of > 20 years on maintenance with oral Methylprednisolone (MPS) can present ESR of > 120 mm/1 hour. It may require 2 months of 5X weekly daily IV therapy to suppress the ESR and clinical BAS indexes to normal.

In some patients the age-adjusted ESR and CRP may need to be applied as it may remain above the standard upper limit of normal ESR and CRP due to age variation, although the CSEs have been normalized. The formula for the age-adjusted upper limit of normal ESR is male age divided by 2 and for female age+10 divided by 2[40]. For CRP the formula is male age divided by 50 and female age divided by 50 plus 0.6[41].

The Objectives

To achieve primary outcome of ASAS20, ASAS40, ASAS70, and secondary outcome of Clinical and Radiological Remission with the SBC-5-IMNs

Prognostic Factors

The most important prognostic factor in Nr-AS is the treatment and IMNs-naivety. Other major determinants of disease outcome are disease duration and disease activity dependent grades of BASRI. When treatment is inadequate (ESR and clinical BAS indexes are not normalized), remission cannot be acquired and the disease progresses to irreversible axial and/or peripheral joint and/or vital organ damage.

Therapeutic principle

The therapeutic principle is to induce Clinical Remission in the shortest period of time by the intravenous (IV) combination of 3 IMNs and weekly polyarticular and multiple intralesional corticosteroids injections without serious adverse effects.

All NSAIDs, ineffective DMARD(s), and oral corticosteroids are stopped at the start of the study. The oral corticosteroid is replaced by an intravenous dose of Methylprednisolone (MPS) equivalent to the oral dose at presentation. This is to prevent withdrawal symptoms of dependent oral corticosteroid. The ASAS improvements and clinical remission is achieved by daily IV CyC+5FU+MTX 5X weekly + polyarticular and multiple intralesional corticosteroids injection once weekly + consolidation by oral therapy for at least 2 years.

Contra-indications

The contra-indications for the application of single or combination drug therapy 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.

When IV MPS is contra-indicated in the previous SBG-5-IMNs, the patients with Diabetes Mellitus and a history of Glucocorticosteroid-induced hyperglycemia, melena and/or hematemesis are not excluded for treatment with the revised SBC-5-IMNs. There is no IV MPS in the revised SBC-5-IMNs.

Exclusion

The IMNs non-naïve patients with Nr-AS with BASRI ≥ 2 should be excluded for treatment with the SBC-5-IMNs as no remission can be achieved. However, ASAS70, ASAS40, and ASAS20 can be obtained. The patient must be IMNs-naïve to IV CYC+5FU+MTX to obtain Remission.

Parenteral or IV MTX/wk is preferred because oral one has lower bioavailability [42]. The maximum number of daily intravenous sessions is 5 times per week to avoid weekly cumulative dose-dependent adverse effects.

Intravenous Dosages

1. CyC [17] 25-100 mg per session+
2. MTX [43] 5-12.5 mg per session once weekly +
3. 5FU 25-100 mg per session (empiric because 5FU was effective in RA [44])

The minimum effective dosages need to be applied in GI-sensitive patients or in those with very low body weight (< 35 Kg). The physiological function of the GI tract, liver, kidneys, and bone marrow in those over 60 years of age has declined at least 25%. Calculating dosages per square meter body surface may be inappropriate in the aged patients. Therefore, the lower range of the dosages of CyC + 5FU + MTX must be applied to avoid dose-dependent adverse effects in advanced aged patients.

The GI-sensitive patients may suffer adverse effects at the 100 mg dose of CyC, 5FU, and 12.5 mg MTX, but may not be at the 75 or 50 or 25 mg or 7.5 or 5 mg MTX dosages. These minimum dosages of the intravenous combination of the 3 IMNs are still effective due to common receptor sites for immunosuppression i.e., activated T-cells, B-cells, and Macrophages.

Intravenous MPS is in fact not absolutely required to achieve remission, but is required to stop oral corticosteroid at presentation and avoid corticosteroid-dependent flare. However, the combination of IV CyC + MPS + MTX achieves: faster remission; reduces the total number of frequencies of intravenous sessions; tide over the dependency on existing oral low or high dose corticosteroids the patients are taking at presentation.

Polyarticular and Intralesional Injections

Polyarticular corticosteroids injection in RA [45] shows efficacy and multiple intralesional corticosteroids infiltration replace the IV MPS in the previous SBC-5-IMNs. These local injections are equivalent effective in Nr-AS. These injections are initiated concomitantly with the IV sessions of the SBC-5-IMNs for persistent axial and peripheral arthritis and intralesional injections for persistent enthesitis, bursitis, tendonitis, and/or Fibromyalgia Syndrome (here is Fibromyalgia a complication of late AS). Some experience is required to feel the painful and tough tendon of enthesitis and painful tiny knobblies focal points of Fibromyalgia.

Intra-articular and intralesional corticosteroids injection are given once weekly with minute amount of the combination of Triamcynolone Acetonide (TA) + Dexamethasone (DxM), and Lignocain until pain relief is obtained. One CC of the combination comprises 0.6 CC (4.8 mg TA) from a 5 CC vial of 40 mg TA + 0.2 CC (1 mg DxM) from 1 CC ampoule of 5 mg DxM + 0.2 CC (0.4 mg Lignocain) from a 2CC ampoule of 2% LNC. Rationale: instant anesthesia up to 4 hours by LNC; efficacy of DxM commences after 4

hours up to 4 days; efficacy of TA is effective after 4 days up to < 6 days. The efficacy of the polyarticular injection lasts at least 10 days.

The polyarticular corticosteroids injections comprise: 0.05-1.0 CC in the hip and sacro-iliac joints (spinal needle 25 G x 3.5") and knee joints (needle 22G x 1.5" or 25G x 1"); 0.5-1 CC in the shoulder by anterior or posterior entree (22G x 1.5" or 25G x 1"), elbow, talo-tibial and talo-calcaneous joints (needle 25G x 1"); 0.25 CC in the mandibular (needle 26G x 0.5"), radial/ulnar-carpal, intercarpal, carpophalangeal, tarsal joints (25G x 1"); 0.125 CC in the MCP, MTP, PIP and DIP joints (needle 26G x 0.5"). Enthesitis and Fibromyalgia are infiltrated with 0.025-0.050 CC of the combination (25G x 1"). The total amount of the cocktail injected once a week is small. With only 35% of this amount absorbed corticosteroids side effects are negligible [46].

When all the big and medium sized joints are injected the total volume is 6-8 CC of the cocktail given once weekly. This is equivalent to 28.8 –38.4 mg TA per week. The 35% leaked into the systemic circulation is 10.1 – 13.4 mg TA per 7 days. The mean daily dose of 1.4 – 1.9 mg TA does not induce significant adverse effects. Even those with a history of melena and/or hematemesis can tolerate this amount of leaked TA if adequately protected with proton pump inhibitor.

Tapering Off Intravenous Therapy

When the ESR, a nonspecific inflammatory indicator, was suppressed to ≤ 20 mm/hour (delayed decline of ESR), the oral therapy was initiated. When ESR achieved a level of ≤ 10 mm (men ≤ 5 mm) the IVT was tapered off as followed: 3X, 2X, and once weekly, once fortnightly, once monthly, and terminated at once 2 monthly. With every doubling of the interval between IV Sessions, the ESR must be checked. When ESR continued its decline, the intervening period was doubled. When the ESR stays stationary or raises again, the IV Session must be repeated again within the same intervening period or stepped back. The oral therapy was continued for at least 2 years. When the IV session was given once fortnightly, the IV MTX was switched to an equivalent oral weekly dose if required.

Remission with oral Drugs

Remission with oral Drugs (RworalDs) is defined when the Oral Therapy sustains Remission for at least 2 years after IV Sessions are tapered off.

Remission without Drug

Remission without Drug is defined when identical status as in RworalDs is maintained after oral therapy is tapered off over a period of 1 year without flare.

Flare

Flare is defined when:

1. ESR increases to ≥ 20 mm (men ≥ 10 mm)
2. Pain ≥ 1
3. BASDAI ≥ 1
4. Swollen joint ≥ 1
5. Tender joint ≥ 1

Early flare within 1 week onset must be immediately suppressed by reinstatement of the IV Sessions. Only 1-2 weeks is required to suppress early flare. Full-blown flare requires the total schedules of the SBG-5-IMNs.

Radiological Normalization of the Joint is defined when Nr-AS with BASRI < 2 is reversed to grade 0 or blurred joint margins reverse to a distinct intact line.

Radiological Remission is defined when Nr-AS with BASRI ≥ 2 , progression is terminated and broken joint margins reverse to an intact sclerotic line with new erosion prevented. Baseline subchondral sclerosis, loss of joint space, joint subluxation, deformity, ankylosis and kyphosis remain in status quo.

In a few cases when the ESR and CRP levels are normal, but patients present with:

1. Pain $\geq 2 - < 4$
2. BASDAI $\geq 2 - < 4$
3. ESR is $\geq 20 - < 40$ mm
4. Swollen joint count ≥ 1
5. Tender joint count ≥ 1

the SBC-5-IMNs may be applied. The BASDAI indexes guide tapering off IV Sessions. The IV sessions are tapered off when the following symptoms and signs are attained:

1. BASDAI < 1
2. Pain ≤ 1
3. Swollen Joint Count ≤ 1
4. Tender Joint Count ≤ 1
5. Patient global assessment of disease activity (0-10) ≤ 1

Persistent high CRP level.

When normal ESR level has been achieved but the CRP is still abnormal, then the source of chronic infections must be investigated. The abnormal CRP level is usually suppressed by the IV sessions of the SBC-5-IMNs within 1-2 months to negative or normal 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 Cephalosporin's or its derivatives can be given to lower persistent CRP level. The Quinolones interact with Immunosuppressants and should be avoided.

The various stages of the application of the SBC-5-IMNs

1. Induction of remission by the daily 5X weekly IV Sessions over a period of 1-2 months with concomitant polyarticular and multiple intralesional injections of minute amount of corticosteroids.
2. Tapering off the IV Sessions is initiated with simultaneous prescription of oral therapy when remission is achieved
3. When Remission has been maintained for at least 2 years, the oral drugs are tapered off over a period of 1 year without flare to Remission without Drug.
4. Radiological Normalization and Radiological Remission is achieved after 2 and 4 years.
5. Long-term maintenance of Remission by immediate re-institution of the IV

Sessions of the SBG-5-IMNs in the initial stage of flare.

Oral Therapy

Oral therapy comprises:

1. Mycophenolate Mofetil (MMF) 500 mg bid-tid [22] solely or when required in combination with the switched over of IV MTX in equivalent oral dose of 5-12.5 mg per week [34] when tapering of the IV Session is initiated.

The addition of oral Cyclosporine (CyS) 50 mg bid-tid [23] may be considered if required to maintain remission.

Low dosages of oral MMF + CyS + MTX not as effective as IV CyC+5FU+MTX+IA+IL corticosteroids injections.

The MMF without or with MTX without or with additional CyS in the dosages low enough to avoid dose-dependent adverse effects is effective only when remission (ESR \leq 20 mm) is achieved. The oral therapy is not initiated together with the IV therapy, because it is not effective when the ESR is \geq 40 mm, CRP is high, and BASDAI \geq 4. Trying to suppress the autoimmune inflammation of Nr-AS with ESR of \geq 40 mm, abnormal CRP and BASDAI \geq 4 by low dosages of oral IMNs is inclined to fail, at least at the low oral dosages of the MMF without or with MTX without or with additional CyS applied within the limit without adverse effects.

No oral MPS and CyC 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.

Hematogenic adverse effects are not or very rarely encountered

1. Dose-dependent hematogenic adverse effects of Thrombocytopenia, Anemia, Leukopenia, or

Pancytopenia is avoided by:

1. low daily intravenous dosages of CyC and 5FU; low weekly cumulative dosages of CyC, 5FU and MTX; low total cumulative dosages of CyC and 5FU; low frequency of exposure to IV CyC, 5FU, and MTX; relative short period of exposure to IV CyC, 5FU, and MTX limited to 6-7 months.
2. The different receptor sites for the different hematogenic adverse effects of leucopenia, thrombocytopenia, anemia, and pancytopenia, to CyC, 5FU, and MTX avoid collectively induced hematogenic side effects.

When hematogenic adverse effects are encountered:

1. leukopenia is normalized by Filgrastim;
2. severe Anemia is normalized by Recombinant Human Erythropoietin;
3. Thrombocytopenia is normalized by Epinephrine + Methylprednisolone;
4. Pancytopenia is normalized by the combination of Filgrastim+Recombinant Human Erythropoietin+ Epinephrine + Methylprednisolone

High frequency of Gastrointestinal (GI) adverse effects

Gastrointestinal adverse effects comprise anorexia, nausea, vomiting, diarrhea, gastritis, GI ulcer and bleeds. The common receptor sites for the different IV CyC, 5FU, and MTX maximize GI adverse effects.

The GI adverse effects can be avoided, prevented, and treated by: ant emetics for nausea and vomiting; spasmolytics for diarrhea; proton pump inhibitors prevent and treat gastrointestinal gastritis, ulcers, and bleeds.

Monitoring of hematogenic, hepatogenic, and renal adverse effects by standard laboratory procedures of the SBC-5-IMNs should be carried out at least once monthly during daily 5X weekly IV sessions. When indicated anytime during the period of the intravenous therapy.

Dosages of IMNs when hematogenic adverse effects appear

Leucocytes	Thrombocytes	Hematocrit	IMNs.	
> 4000	> 100,000	> 35	100%	dosages
4,000-2,500	100,000-50,000	30-35	50%	dosages
< 2,500	< 50,000	< 30	0%	dosages

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 [47]. Epinephrine in 100-200 CC 0.9% NaCl. Adrenaline is an inherent component of our body and is a life saving drug. The very slow drip-rate depends on the appearance of palpitation (tachycardia) 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 sequences of serial drugs, while temporary stopping the cause of the allergy.

Co-morbidity

Co-morbidity or associated conditions such as Hypertension, Diabetes Mellitus, Atherosclerosis, 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 Ibandronate Acid [48,49,50] with concomitant daily oral Calcium and Minerals supplements can treat severe osteoporosis (Tscore > - 4) faster than oral Biphosphonates and/or Laroxyphene. 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 for any reason. Dropouts never achieve remission, but nevertheless, considerable improvements still occur in these irregular treated patients.

Outcome Measures

The standard primary endpoint measured is ASAS20, and secondary endpoints are

ASAS40, ASAS70, Health-related Quality of Life or SF-36, Rworalds, Rwd, and Radiological Remission.

The proposed revised guidelines of the SBC-5-IMNs are an ever-evolving initiative, which requires continuous assessments, refinements, and revisions based on new experience gained in open-label or inception cohort observational studies and in Randomized Controlled Trials (RCT).

Summary of SBC-5-IMNs

The SBC-5-IMNs is a two-steps therapy. The first step is the daily 5X weekly IV CyC + 5FU + MTX, which is initiated concomitantly with polyarticular and multiple intralesional corticosteroids injections in persistent arthritis and enthesitis etc. When remission is achieved, the IV Session is tapered off and polyarticular and multiple intralesional injections remain optional when required. The second step is prescription of the oral MMF solely without or with MTX (switched over from IV MTX once weekly) equivalent to the IV dose. The CyS, when required is additional is prescribed. The oral IMN(s) is taken for at least 2 years during Rworalds for consolidation, before tapering off is attempted over a period of 1 year without flare to Rwd. As long as the attachments of T-cell by Antigen Presenting Cells (APC) and the co-stimulatory pathways, which activate the APC-T-cells complex, are not blocked permanently, there is a lifetime risk for flares.

Conclusion: the revision entails no IV MPS in the SBC-5-IMNs. The IV MPS is replaced by the polyarticular injections and intralesional infiltration of corticosteroids in the enthesitis, tendonitis, bursitis, Fibromyalgia, etc.

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Appendix I

Definition

NSAID-refractory-AS is defined when after treatment with at least 2 different NSAIDs over a period of at least 2 months, ASAS20 is not obtained, ESR, CRP, and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) Score do not improve or get worse compared with baseline.

Active disease is defined as BASDAI ≥ 4 , ESR ≥ 40 mm (men ≥ 30 mm) and CRP [9] ≥ 3 mg%.

Remission is defined when ESR and CRP have declined to ≤ 10 mm (men ≤ 5 mm), and BASDAI, BASFI, BASG, and BASMI are mean < 1 (scale 1-10).

Remission with oral drugs (RworalDs) is defined when remission is maintained with oral drugs.

Remission without Drug (RwD) is defined when remission persists without flare and without drug.

Radiological Normalization is defined for those with BASRI < 2 when normalization of the axial and/or peripheral joint(s) are obtained.

Radiological Remission is defined for those with BASRI ≥ 2 when progression of baseline calcification is terminated and erosion healed, new erosion is prevented and in status quo are baseline:

spine: sclerosis, syndesmophytes; squared and fused vertebrae, and kyphosis.

hip joint: sclerosis, osteophytes; loss of joint space; bone on bone apposition; protrucio-acetabuli; and bone deformity.

Flare is defined when BASDAI rises to ≥ 1 , ESR ≥ 20 mm and CRP ≥ 3 mg%.

Appendix II

Appendix AS

Diagnosa Ankylosing Spondylitis (AS) ditegakkan dengan Modified New York Criteria

Modified New York Criteria ada dalam makalah

Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis a proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.

Hasil terapi AS diukur dengan:

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Garrett S, Jenkinson T, Kennedy LG et al. A New Approach to defining Disease Status in Ankylosing Spondylitis: The Bath Ankylosing Spondylitis Disease Activity Index . *J Rheumatol* 1994;21:2286-2290.

Bath Ankylosing Spondylitis Functional Index (BASFI)

Calin A, Garrett S, Whitelock H et al. A New Approach to Defining Functional Ability in Ankylosing Spondylitis: The Development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;21:2281-2285.

Bath Ankylosing Spondylitis Patient Global Score (BAS-G)

Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). *Br J Rheumatol* 1996;35:66-71.

Bath Ankylosing Spondylitis Spinal Mobility Index (BASMI)

Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol* 1994;21:1694-8.

BATH ANKYLOSING SPONDYLITIS RADIOLOGY Spinal INDEX (BASRI-s)

Kirsten Mackay, Christopher Mack, Sinead Brophy et al. THE BATH ANKYLOSING SPONDYLITIS RADIOLOGY INDEX (BASRI). *Arthritis Rheum* 1998;41:2263-2270.

BATH ANKYLOSING SPONDYLITIS RADIOLOGY Hip INDEX (BASRI-h)

MacKay K, Brophy S, Mack C, Doran M, Cali A. The development and validation of a radiographic grading system for the hip in ankylosing spondylitis: the bath ankylosing spondylitis radiology hip index. *J Rheumatol* 2000 27:2866-72.