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Proposed Revised Step-down Bridge Combination of 5 Immunosuppressants in the Therapy of Autoimmune Diseases

Rheumatoid Arthritis

Introduction

Rheumatoid Arthritis (RA) is the most notorious chronic progressive autoimmune disease. There is continuous progression of joint destruction^{1,2,3}. Almost 99% of the patients show joint erosions after 17 years in a selective sample of patients⁴. The increase of X-ray abnormalities reflects loss of function⁵. In a 10-year prospective observational study of the Step-down Bridge Combination of 4 Immunosuppressants (SBC-4-IMNs) in the treatment of Rheumatoid Factor (RF) Positive Rheumatoid Arthritis (RF+ RA), radiological remission was observed in 93% of the patients⁶. Disease activity, disease-duration, grades of erosions and IMN-naivety determine outcome of RF+ RA. Single drug therapy with one of the Immunosuppressants (IMNs) or DMARDs is not or less effective in moderate or severe RA⁷.

Biologic Response Modifiers

The small minority who achieves ACR70 (around 20%) with the Biologic Response Modifiers (BRMs)⁸ may be due to only TNF-*alfa* being antagonized⁹. This leaves all the cytokines, rheumatoid factors (RFs), (IgG and IgM) and all autoantibodies uninhibited to continue the inflammatory cascade. Consequently: no normal level of ESR¹⁰ and CRP¹¹ are obtained; radiological joint normalization in those with \leq grade 2 erosion and radiological remission in those with \geq grade 2 erosions are not reported in these studies⁶. However, delayed or less radiographic progression after 2 years of continuous treatment with Infliximab compared to conventional therapy has been suggested in a small study¹². After cessation of therapy, almost all patients experienced a relapse within a few weeks to several months¹³. Thus, it seems probable that BRMs must be administered continuously for long-term or lifetime in most RA patients to achieve permanent inhibition of TNF-*alfa*.

The annual expenses for therapy of RA with the BRMs combined with Methotrexate are \$15,000.00 to \$25,000.00¹⁴. 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.

In developed countries with health insurance and social securities, it is hardly possible to get RA 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 RA. Only very few patients with RA in the Third World can afford the long-term or lifetime BRMs without or with Methotrexate. The BMRs are Remicade (Infliximab); Enbrel (Etanercept); Kineret (Anakinra); Humira (Adalimumab); Mabtera (Rituximab). A less expensive alternative therapy must be derived from existing IMNs in the Third World that shows varying efficacies in RA.

Immunosuppressants

One IMN will not suppress the various aspects of autoimmune inflammation, as reflected in the TNF-*alfa* and different types of cytokines, RFs, and all autoantibodies provoking the inflammatory cascade. Therefore, combination of IMNs is justified in the treatment of RA. The SBC-5-IMNs in the Therapy of refractory RA is a combination of generic IMNs. The combination of DMARDs comprising oral MPS, Hydroxychloroquine, Sulfasalazine, NSAIDs, is 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\$2000.00 - 3,000.00. The second and third year is US\$1,000-2000 for oral drugs. In Remission without Drug (RwD) there is no drug expenses after 3 years. Those in Remission with oral Drugs (RworalDs) require long-term maintenance with MMF, which cost less than US1000.00 annually. This is obviously less expensive than the annual treatment costs with biologic response modifiers of US\$15,000.00 to US\$25,000.00¹³ 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.

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, RFs, and all autoantibodies by the IV Cyclophosphamide+MPS/5-Fluorouracil+Methotrexate (CyC+MPS/5FU+MTX). Suppression of the secretion of the TNF-*alfa*, all cytokines, RFs, and autoantibodies may explain achievement of ACR20, ACR50, ACR70, ESR ≤ 10 , clinical remission, radiological joint normalization and radiological remission in the majority of patients with RA.

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

1. Pain (0-10) ≥ 4
2. Erythrocyte Sedimentation Rate (ESR)² of ≥ 40 mm (men ≥ 30 mm),
3. Swollen Joint Count ≥ 1
4. Tender Joint Count is ≥ 1

The RA patients with erosion < grade 2 or \geq grade 2, but:

1. Pain is ≥ 2 - <4
2. ESR is ≥ 20 - < 40 mm
3. Swollen joint count ≥ 1

4. Tender joint count ≥ 1

Radiological joint erosions are not always progressive as a small percentage of RA patients may enjoy spontaneous Remission (4-26% depending on cohort sample selection). 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.

OMERACT7 defines Clinical Remission¹⁵ when:

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

OMERACT7 Proposed Minimum Disease Activity (MDA)¹⁵ for RA

The MDA is defined when 5 of the 7 WHO-ILAR Core Set Endpoints (CSEs) are met:

1. Pain ≤ 2
2. Swollen Joint Count ≤ 1
3. Tender Joint Count ≤ 1
4. Health Assessment (HAQ, 0-3) ≤ 0.5
5. Physician global assessment of disease activity (0-10) ≤ 1.5
6. Patient global assessment of disease activity (0-10) ≤ 2
7. ESR ≤ 20

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 ($> \text{MDA}$). This is in particular true in chronic longstanding RA. 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 CSEs 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 2¹⁶. For CRP the formula is male age divided by 50 and female age divided by 50 plus 0.6¹⁷.

The Objective

The objective of the SBG-5-IMNs is to induce and maintain MDA, clinical and radiological remission by total suppression of the formation of TNF-*alfa* and all Cytokines, RFs, and all autoantibodies in autoimmune diseases.

The Rationale

Radiographic remission in RA has occurred in 28% in selective sample of patients¹⁸; progression of baseline erosion has been terminated and broken joint margins reverse to an intact one with new erosion prevented by the SBC-4-IMNs⁶. When irreversible joint damage occurs, the ultimate option left may be reconstructive joint surgery or total joint replacement. For the Third World one of the options left is the SBC-5-IMNs for prevention of joint deformity and

surgery.

Prognostic Factors

The most important prognostic factor in RA is the treatment and IMNs-naivety. Other major determinants of disease outcome are disease duration and disease activity dependent grades of erosion⁶. When treatment is inadequate (ESR and CSEs are not normalized), MDA and remission cannot be acquired and the disease progresses to irreversible joint and/or vital organ damage.

Therapeutic principle

The therapeutic principle is to induce MDA in the shortest period of time by the intravenous (IV) combination of 3 IMNs and 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. The MDA is achieved by daily IV CyC+MPS/5FU+MTX 5X weekly + polyarticular and multiple intralesional corticosteroids injection once weekly.

Contra-indications

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

Intravenous Methylprednisolone is contra-indicated, but Patients with Diabetes Mellitus and a history of Glucocorticosteroid-induced hyperglycemia, melena and/or hematemesis are not excluded for treatment with the revised SBG-5-IMNs. There is no IV MPS in the revised SBC-5-IMNs, except those under treatment with oral corticosteroids at presentation

Exclusion

The IMNs non-naïve patients with RA with \geq grade 2 erosions should be excluded for treatment with the SBG-5-IMNs as no MDA can be achieved. However, ACR70, ACR50, and ACR20 can be obtained. The patient must be IMNs-naïve to IV CYC+5FU+MTX to obtain MDA and Clinical Remission.

Intravenous MTX/wk is preferred because oral one has lower bioavailability¹⁹. The maximum number of daily intravenous sessions of CyC+5FU is 5 times per week to avoid weekly cumulative dose-dependent adverse effects.

Intravenous Dosages

1. CyC²⁰ 25-100 mg per session+
2. MTX²¹ 5-12.5 mg per session once weekly +
3. 5FU 25-100 mg per session²²

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 immuno-suppression i.e., activated T-cells, B-cells, and Macrophages.

Intravenous MPS is in fact not absolutely required to achieve MDA, but is required to stop oral corticosteroid at presentation and avoid corticosteroid-dependent flare. However, the combination of IV CyC + MPS + MTX achieves: faster MDA; 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.

Intraarticular and Intralesional Injections

Polyarticular corticosteroids injections²³ and multiple intralesional corticosteroids infiltration replace the IV MPS in the previous SBC-5-IMNs. These injections are initiated concomitantly with the IV sessions of the SBC-5-IMNs for persistent arthritis and intralesional injections for persistent enthesitis, bursitis, tendonitis, discitis, and/or Fibromyalgia Syndrome (here is Fibromyalgia a complication of late rheumatoid arthritis). Some experience is required to feel the painful and tough tendon of enthesitis and painful tiny knobbly focal points of Fibromyalgia.

Intra-articular (IA) and intralesional (IL) corticosteroids injection are given once or twice weekly with minute amount of the combination of Triamcynolone Acetonide (TA) + Dexamethasone (DxM), and lignocain until pain relief is obtained. One CC IA+IL 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% Lignocain Rationale: instant anesthesia up to 4 hours by Lignocain; efficacy of DxM commences after 4 hours up to 4 days; efficacy of TA is effective after 4 days up to < 6 days.

The polyarticular corticosteroids injections comprise: 0.05-1.0 CC in the hip (spinal needle 25 G x 3.5") and knee joints (needle 22G x 1.5" or 25G x 1"); 0.5 CC in the shoulder (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 4.8 mg TA+1 mg DxM+0.4 mg Lignocain per CC (needle 25G x 0.5"). The total amount of the cocktail injected once a week is small. With only 35% of this amount absorbed corticosteroids side effects are negligible²³.

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. 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. Very rarely are all the big peripheral joints injected at 1 session.

Tapering Off IV Therapy

The 5X weekly IV Sessions is continued until ESR is \leq 20 mm and the MDA is achieved. Then the oral MMF without or with oral MTX equivalent to its IV dose are prescribed. When required additionally CyS is added. When the MDA is achieved and the oral therapy is initiated, the IV sessions are tapered to once weekly, once fortnightly, once monthly, and terminated once 2-monthly. The RworlDs is maintained for at least 2 years and tapered off one by one during the third year to Remission without flare and Remission without Drug (RwD) when the ESR \leq 10 mm.

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. After 2 years the oral IMNs are tapered off over a period of 1 year without flare to Remission without Drug (RwD).

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 Remission returns to \geq MDA. 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 RA with erosion $<$ grade 2 is reversed to grade 0 or blurred joint margins reverse to a distinct intact line.

Radiological Remission is defined when RA with \geq grade 2 baseline erosion, the latter 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, and ankylosis remain in status quo⁶.

In a few cases when the ESR and CRP levels are normal, but patients present with $>$ MDA, the SBC-5-IMNs may be applied. The following 5 of the 7 WHO-ILAR CSEs then guide tapering off IV Sessions when the MDA is achieved:

1. Pain ≤ 2
2. Swollen Joint Count ≤ 1
3. Tender Joint Count ≤ 1
4. Physician global assessment of disease activity (0-10) ≥ 1.5
5. Patient global assessment of disease activity (0-10) ≥ 2

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 Cephalosporines 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 MDA by the daily 5X weekly IV Sessions over a period of 1-2 months with concomitant polyarticular and multiple intralesional infiltrations of minute amount of corticosteroids.
2. Tapering off the IV Sessions is initiated with simultaneous prescription of oral therapy when MDA is achieved
3. When Remission is achieved and 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 after 2 and 4 years. Radiological Remission is achieved
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-tid²⁵ solely or when required in combination with the switched-over of IV MTX in equivalent oral dose of 5-12.5 mg per week²⁴ when tapering of the IV Session is initiated.

The addition of oral Cyclosporine (CyS) 50 mg bid-tid²⁶ may be considered if required to maintain MDA.

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 MDA (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 CSEs are not normalized and stabilized by the intravenous therapy.

Trying to suppress the autoimmune inflammation of RA with ESR of \geq 40 mm, abnormal CRP and abnormal CSEs 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 are 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: antiemetics 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 CC²⁷.

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 sequence 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 RA. Osteoporosis can be due to corticosteroids abuse or menopause, or advanced age (> 60-70 years), or RA or immobility or any one, two, three or all four factors combined. Intravenous Ibandronate Acid^{28,29,30} 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 MDA or Remission, but nevertheless, considerable improvements still occur in these irregular treated patients⁷.

Outcome Measures

The standard primary outcome measures applied are ACR20, ACR50, ACR70, Health-related Quality of Life or SF-36. For secondary outcome the MDA, Rworalds, Rwd, Radiological Joint Normalization, and Radiological Remission can be applied.

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 or infiltration. When Minimum Disease Activity (MDA) is achieved 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 Remission with oral Drugs (Rworalds) for consolidation, before tapering off is attempted over a period of 1 year without flare to Remission without Drug (RwD). As long as the attachment of T-cell by Antigen Presenting Cells (APC) and the co-stimulatory pathways, which activate the complex APC-T-cells are not blocked permanently, there is a lifetime risk for flares.

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