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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 autoimmune inflammation by 5X weekly daily intravenous (low and safe dosages) combination of Cyclophosphamide + 5-Fluorouracil + weekly Methotrexate [1].
2. Suppression of activated Synovial Fibroblasts [2] 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).

The rationale of polyarticular injections is instant local 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, before pain is abolished. No intravenous and 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 Methotrxate is still effective.

John Bridge Therapy is only applied in Lupus Nephritis and Nephrotic Syndrome refractory to single or combination drugs therapy of oral NSAIDs, Azathioprine, Methylprednisolone, and Cyclophosphamide or pulses of intravenous Methylprednisolone and Cyclophosphamide.

Lupus Nephritis or Nephrotic Syndrome

Introduction

Single drug therapy is mostly adequate in renal biopsy WHO Class I and II Lupus Nephritis (LN) [6]. Single drug therapy in LN in biopsy Class III, V, and in particular Class IV is less or not effective. One Immunosuppressant (IMN) cannot suppress all aspects of autoimmune inflammation such as the various autoantibodies and different cytokines in moderate to severe LN. The Step-down Bridge Combination of 5 IMNs (SBC-5-IMNs) is not required in Class I, II, and VI renal biopsy. In Class VI nothing helps, except renal transplantation and administration of the SBC-5-IMNs is obviously inappropriate.

The SBC-5-IMNs is a combination of 5 generic IMNs and are less expensive. The common receptor sites for suppression of the various auto-antibodies formation by B-cells, TNF-*alfa* and the various cytokines by the Macrophages with the combination of minimum effective dosages of IMNs maximizes immunosuppressive efficacy.

Inadequately treated LN in Class III and V, and in particular Class IV is inclined to progress to Nephrotic Syndrome, End Stage Renal Disease, and early mortality mostly by infection. Renal disease as a complication of severe SLE still cause major morbidity and some mortality for around 30-40 in biopsy Class IV [7]. Therefore, the application of the SBC-5-IMNs is justified in LN Class III to V. Nevertheless, therapy of Lupus LN has achieved Remission with or without Drug. The latter are previously called "Treatment-free Remission" [8,9,10]. Early diagnosis and treatment improved endpoint of LN.

The Step-down Bridge Combination of 5 Immunosuppressants

Based on the abovementioned considerations JD through trials and errors over a period of more than 5 years since 1992, has concocted the SBC-5-IMNs for therapy of Autoimmune Diseases inclusive of LN. The SBC-5-IMNs is a two-steps treatment procedures comprising:

initial 5X weekly intravenous (IV) Cyclophosphamide (CyC) + Methylprednisolone (MPS) + Methotrexate (MTX); when required with simultaneous once weekly polyarticular injections and infiltrations of a combination of Lignocain (LNC) + Triamcynolone (TA) + Dexamethasone (DxM) into tendinitis, bursitis, focal points of fibromyalgia. When ESR has achieved a level of \leq 20 mm (men \leq 10 mm), the step-down oral MMF is initiated without or with additional MTX and/or Cyclosporine (CyS).

Biologic Response Modifiers

The Biologic Response Modifiers such as Infliximab (Remicade), Etanercept (Enbrel), and Adalimumab (Humira), 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. [11] Therefore, anti-TNF-*alfa* therapy should not be applied in patients with Lupus. When biopsy-proven LN Class III, IV, and V appears during the application of the TNF-*alfa* antagonists, the Biologic Response Modifiers must be immediately withdrawn and the SBC-5-IMNs prescribed. Biologic 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 Biologic Response Modifiers oral IMN is adequate.

The Objective

The objective of the SBC-5-IMNs is to induce and maintain clinical and histological remission in LN.

The Rationale

The underlying rationale for early application of the SBC-5-IMNs in LN is: once renal damage occurs, progressive damage ensues when disease activity remains high (Systemic Lupus Activity Measure or SLAM Score \geq 4); initial high ACR Damage Index is associated with high mortality rate [12]; significant continuous progression of vital organ damage occurs when LN is treated with oral corticosteroids over a period of >15 years [13].

Prognostic Factors

The most important prognostic factors in LN are: early diagnosis; the treatment itself; early treatment; Chronicity Index < 5 [12]; renal biopsy Class III, IV, and V. These are emergencies when renal histological changes are still reversible [14]. WHO Class VI is irreversible histological damage, when nothing helps. [15]

Definition

Remission of Lupus Nephritis is defined when the mean SLAM Score is < 1, ESR \leq 10 mm (men \leq 5 mm), and the 24 hours urinary Micro-Albuimne is \leq 30 mg.

Remission with oral Drugs (RworalDs) is defined when remission is maintained by oral IMNs.

Remission without Drug (RwD) is defined when the oral IMNs of in RworalDs is tapered off over a period of 1 year without flare.

Flare is defined when the mean SLAM Score and ESR increase to \geq 1 and \geq 20 mm during RworalDs and RwD.

Dropout is defined for the treated patients who do not complete the therapy schedules for any

reason.

Age-adjusted ESR and CRP

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, although SLAM Score maybe < 1 . The formula for the age-adjusted upper limit of normal ESR in male is age divided by 2 and female age+10 divided by 2 [16]. For CRP the formula is male age divided by 50 and female age divided by $50+0.6$ [17].

Therapeutic Principle

The therapeutic principle is to achieve total suppression of autoimmune inflammation (remission) at the shortest possible period of time without serious adverse effects by IV therapy (IVT) + weekly polyarticular injections and intralesional infiltrations corticosteroid combination + consolidation by oral therapy for at least 2 years. As mentioned before the IVT comprised MPS + CyC + MTX.(IV Triple 3 or IVT-3)

When remission is achieved (see definition) the IVT is tapered off to Remission with oral Drugs (RworalDs) for at least 2 years for consolidation. After 2 years without flare the oral drugs are tapered off over a period of 1 year without flare to Remission without Drug (RwD) to avoid longer exposure to the combination of IVT-3.

Flare during RworalDs and RwD must be immediately suppressed by several sessions of the IVT-3 within 1 week of onset. Full-blown flare requires the total schedule of the SBC-5-IMNs.

Indication for treatment of LN with the SBC-5-IMNs when renal biopsy is:

1. WHO Class IV Or
2. Class III and V with SLAM Score ≥ 4 and ESR ≥ 40 mm

Contra-indications

The contra-indications for the application of single or combination drug therapy of LN with immunosuppressant such as CyC, MPS, MTX, Mycophenolate Mofetil (MMF), and Cyclosporin (CyS) are obvious. The inserted leaflets in the package of each individual immunosuppressant from the manufacturers are self-explanatory.

Methylprednisolone is replaced by 5-Fluorouracil

Diabetes Mellitus and a history of melena and/or hematemesis are not excluded for treatment by the SBC-5-IMNs. Empirically, the MPS is replaced by 5-Fluorouracil (5FU) to avoid corticosteroid-induced hyperglycemia and flare of melena and/or hematemesis.

When no oral Prednisolone is administered at presentation, there is no need to give intravenous MPS. Five-Fluorouracil replaces MPS.

The Intravenous Therapy

The contemporary standard daily 5X weekly intravenous immunosuppressive combination therapy is:

1. CyC + MPS + weekly MTX with termination of oral corticosteroids when patients are on high dosages of Methylprednisolone or Prednisone or Prednisolone at presentation.
- Or
2. CyC + 5FU + weekly MTX without IV MPS and without oral corticosteroids when IV MPS is contra-indicated

Intravenous weekly MTX is preferred because oral one has lower bioavailability [18]. The maximum

number of daily intravenous sessions is 5 times per week to avoid high weekly cumulative dose-dependent adverse effects. In CyC-refractory or CyC non-naïve LN, Ifosfamide is an analog, which replaces CyC.

Mortality of LN with renal biopsy WHO Class IV is still 30-40% in the First and Second World. The National Institute of Health, Bethesda, Maryland, USA, recommends IV MPS + CyC and oral MMF + CyS for treatment. This solves the dilemma of prescribing more than 15 years oral corticosteroids in LN. Corticosteroid-induced adverse effects in vital organs appears after more than 15 years treatment with oral corticosteroids [13].

Intravenous Dosages

1. MPS [19] 25-125 mg per session
2. CyC [19] 25-100 mg per session+
2. MTX [20] 5-12.5 mg per session once weekly +
3. 5FU* 25-100 mg per session) +

***Empirical application**

The minimum dosages need to be applied in sensitive patients or in those with very low body weight (< 30 Kg). The physiological function and anatomical resilience of the GI tract, liver, kidneys, and bone marrow in those over 60-70 years of age has declined at least 25%-30%. Calculating dosages per square meter body surface may be inappropriate in the aged patients.

Therefore, the lower range of the dosages of CyC/5FU + MPS + MTX must be applied to avoid dose-dependent adverse effects in advanced aged patients. The sensitive patients may suffer adverse effects at the 100 mg dose of CyC, 5FU, 12.5 mg MTX, and 125 mg of MPS, but not at the 75 or 50 or 25 mg or 5 mg dosages respectively. These minimum dosages of the IVT-3 are still effective due to common receptor sites for immunosuppression by combination of IMNs.

Methylprednisolone is in fact not absolutely required to achieve Remission, but relatively required to taper off and achieve Remission in patients still on high dose oral corticosteroids at presentation. However, the combination of CyC + MPS+ weekly MTX achieves: faster efficacy; reduces the total number of frequencies of intravenous sessions; tide over the dependency on existing oral low or high dose corticosteroids at presentation when the latter are terminated. It is possible to terminate directly the oral corticosteroids at presentation and switch over to equivalent dosages IV MPS.

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

1. Induction of Remission by the daily 5X weekly IVT-3 Sessions over a period of 2-4 months with concomitant polyarticular and multiple intralesional infiltrations of minute amount of Triamcynolone Acetonide (TA) + Lignocain (LNC) + Dexamethasone (DxM) if arthritis, enthesitis, tendinitis, myalgia, and fibromyalgia persists.
2. When the ESR achieved a level of ≤ 20 mm (men ≤ 10 mm) prescription of oral therapy is initiated.
3. When ESR is ≤ 10 mm and SLAM Score < 1, the IVT-3 is tapered off to remission with oral drugs.
4. After Rworalds is maintained for at least 2 years and 24 hours urinary Micro-Albumin is ≤ 30 mg, the oral drugs are tapered off over a period of 1 year without flare to RwD.
5. Renal histological normalization is achieved after 2-4 years.
6. Long-term maintenance of RwD by immediate re-institution of the IVT-3 Sessions of the SBG-5-IMNs in early flare.

Oral Therapy

The Oral Therapy of the SBC-5-IMNs is to maintain the remission achieved by the IVT-3. Oral therapy comprises:

1. MMF [21] 250-500 mg bid-tid +
2. MTX [20] 5-12.5 mg per week when* the intravenous therapy is terminated +
3. CyS [22,23] 25-50 mg bid-tid*.

*when required

The MMF + CyS + MTX in the dosages low enough to avoid adverse effects is effective only when the ESR \leq 20 mm, SLAM Score < 1 , and Proteinuria is negative (Esbach). Trying to suppress the autoimmune inflammation of LN with ESR of more than 40 mm/1 hour, SLAM Score ≥ 4 , and Proteinuria $\geq 3+$, by low dosages of oral MMF + CyS + MTX is inclined to fail, at least at the low oral dosages of CyS + MMF + MTX/wk applied within the limit without adverse effects.

No oral Methylprednisolone [24] and Cyclophosphamide [24] are prescribed for reasons of more severe and more frequent adverse effects compared with IV administration. Intravenous therapy achieves faster, maximum, and long-lasting efficacy with minimum adverse effects compared with oral therapy, which generates slower, minimum, and short-lasting efficacy with maximum adverse effects.

The SBC-5-IMNs is most effective when the patients with LN are IMNs-naïve where Rwd is achieved. In those who are IMNs non-naïve Rworalds is obtained and maintained long-term.

Monitoring of Adverse Effects

The different receptor sites for different hematogenic adverse effects of the CyC, 5FU, and MTX like Thrombocytopenia, Leucopenia, Anemia or Pancytopenia are minimized by individual minimum effective dosages. However, the common receptor sites of the CyC/5FU + MPS + MTX and Oral MMF + CyS maximizes GI adverse effects. However, GI adverse effects nowadays can be treated and prevented by Proton Pump Inhibitors or derivatives.

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

Pancytopenia are avoided by: low daily intravenous dosages of CyC/5FU; low weekly cumulative dosages of CyC/5FU; low total cumulative dosages of CyC/5FU; low total frequency of IV sessions of CyC/5FU; short exposure to CyC/5FU limited to 5.5-7.5 months. The different receptor sites for the different hematogenic adverse effects of the individual CyC/5FU, MTX, CyS, and MMF avoid collectively-induced hematogenic side effects by its combination.

When hematogenic adverse effects are encountered: leukopenia is normalized by Filgrastim; severe Anemia is normalized by Recombinant Human Erythropoietin; severe Anemia is normalized by Recombinant Human Erythropoietin; Thrombocytopenia is normalized by Epinephrine + Methylprednisolone; Pancytopenia is normalized by the combination of Filgrastim + Recombinant Human Erythropoietin + Epinephrine + Methylprednisolone.

Due to common receptor sites the SBC-5-IMNs collectively-induced GI adverse effects in 55.5% when not protected. When prevented the GI adverse effects are 25.0% [20]. Intensive prevention reduces GI adverse effects to $< 1\%$, but the costs are high for intravenous Proton Pump Inhibitors. These GI adverse effects can be avoided, prevented, and treated by:

spasmolytics for diarrhea; antiemetics for nausea and vomiting; proton pump inhibitors and/or H₂ antagonists prevent and treat gastritis, ulcers, and bleeds.

Preceding the immunosuppressants with intravenous Granisetron, H₂ Antagonists and/or Proton Pump Inhibitors, and spasmolytics has minimized the GI adverse effects. This was achieved by intensification of prevention of GI adverse effects such as nausea, vomiting, and diarrheas. H₂ Antagonist and/or Proton Pump Inhibitors intravenous drips preceded those with a previous history of GI ulcer. Emerging nausea and vomiting induced by immunosuppressants are suppressed and prevented by Granisetron.

Monitoring of adverse effects by standard laboratory procedures of the combination of immunosuppressants should be carried out at least once monthly. When indicated anytime during the period of the IVT.

Hematological monitoring of adverse effects and dosages of IMNs

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

Dosage of Methylprednisolone remains 100%.

In Lupus leucopenia, thrombocytopenia, and anemia are common. These are not necessary induced by the IMNs. An increase blood count due to the SBC-5-IMNs indicates that the low leucocytes, thrombocytes, and hematocrit count are lupus induced. Lowering of the blood count after SBC-5-IMNs shows IMNs toxicity.

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 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. All the contraindications and safety precautions must be observed before the administration of intravenous Epinephrine [25]. 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.

Polyarticular and intralesional injection and infiltration

Intraarticular (IA) injections for persistent chronic arthritis and intralesional injections for enthesitis, bursitis, tendonitis, discitis, and/or Fibromyalgia 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 IA combination.

These local injections are effective in RA [26] and are equally effective in LN with musculoskeletal manifestation. 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, discitis, and/or Fibromyalgia Syndrome (here is Fibromyalgia a complication of late LN). Some experience is required to feel the painful and tough tendon of enthesitis and painful tiny knobby focal points of Fibromyalgia.

Intra-articular (IA) and intralesional (IL) corticosteroids injection are given once weekly with minute amount of the combination of TA + DxM, and LNC until pain relief is obtained. One CC

of 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 LNC) 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 polyarticular injection is at least effective for 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 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 IA+IL combination (25G x 1"). The total amount of the cocktail injected once weekly is small. With only 35% of this amount absorbed corticosteroids side effects are negligible [26].

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 the ESR continued its decline to ≤ 10 mm, SLAM Score < 1 , and negative proteinuria, the IV sessions 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 rises 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.

The Rworalds must be consolidated for at least 2 years by immediate suppression of early flare by reinstatement of IVT and monthly monitoring of the 24 hours urinary Micro-Albumin. Thereafter, Oral Therapy is tapered off over a period of 1 year without flare to Rwd. If 2 flares appear during repeated tapering of oral drugs, the Rworalds should be maintained medium to long-term.

Additional therapies in Nephrotic Syndrome

1. Generalized edema due to excess body fluids because of hypoalbuminemia should be immediately removed by daily IV infusion of human albumin to attain normal serum level.
2. Pericardial, pleural, and abdominal effusion will be reabsorbed when the serum albumin has achieved normal level,
3. Mineral imbalance should be immediately restored by IV drips of modified Ringer's Solution
4. Uremia can be lowered by essential ketoacids (Ketosteril)
5. Autoimmune pericarditis and pleuritis will be totally suppressed by the SBC-5-IMNs in a relative short period of time.
6. Intravenous administration of roburantia and nutrition are required when the patient cannot take oral or nasogastric fluids and nutrition.

Co-morbidity

Co-morbidity or associated conditions such as Hypertension, Diabetes Mellitus, Artherosclerosis, Neuropathy, Osteoporosis, Avascular Osteonecrosis, osteoporosis in particular due to previous

corticosteroids administration etc., must be treated simultaneously with the LN with IV Ibandronate 2 mg per session.

Outcome Measures

The choice of Outcome Measures is left to the discretion of the main investigator. There are 6 validated outcome measures for SLE.

Summary of SBC-5-IMNs

The SBC-5-IMNs is a two-steps therapy. The first step is the daily 5X weekly IV CyC + MPS/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 attachment 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 replacement of IV MPS by 5FU in the SBC-5-IMNs.

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This treatment regimen is an ever-evolving investigational therapy, which requires a dynamic continuous assessment, refinement, and revision based on new experience gained in open-label or inception cohort observational studies and in Randomized Controlled Trials (RCT).

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