

Postgraduate Medical Information for the Medical Practitioners

Breakthrough in the Treatment of NSAID-refractory Ankylosing Spondylitis by the Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants

Frequent Asked Questions

When your Ankylosing Spondylitis (AS) proved NSAID-refractory to standard therapy, what are the treatment options?

Standard therapy of AS is COX1 or COX2 NSAID and physiotherapy. The best treatment option is the Step-down Bridge Protocol of Intravenous and Oral Combination of 6 Immunosuppressants (SBP-6-IMNs) in the short, medium, and long-term.

Is the SBP-6-IMNs Symptoms or Disease Control?

The SBP-6-IMNs in the therapy of NSAID-refractory AS is directly Disease Control and Symptoms Control. When the disease is controlled symptoms disappeared. There is no need for relieve of pain by analgesics and COX1 and COX2 NSAIDs when the disease is directly controlled by the SBP-6-IMNs.

NSAID-refractory AS is defined when after treatment with at least 2 different NSAIDs over a period of at least 2 months, the Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), and Bath Ankylosing Disease Activity Index do not improve or get worse significantly compared with baseline.

In a relative short period of time NSAID-refractory AS is controlled (Disease in Control) by the SBP-6-IMNs.

The **SBP-6-IMNs** comprises Intravenous (IV) Cyclophosphamide + Methylprednisolone + 5-Fluorouracil + weekly Methotrexate and oral Mycophenolate Mofetil + Cyclosporine + weekly Methotrexate.

The schedules of the SBP-6-IMNs application in patients with NSAID-refractory AS are:

1. Initially, intensive daily application of the SBP-6-IMNs is limited to 5X weekly (1-2 months).
2. Declining frequency of intravenous therapy to 3, 2, and once weekly in accordance with the declining ESR levels of < 40 mm, < 30 mm, and < 25 mm respectively (1-2 months)
3. After ESR and CRP are suppressed to < 20 mm (men < 10 mm) per 1 hour and < 3 mg%, Disease in Control is achieved (1-2 months).
4. During Disease in Control the IV therapy is tapered off (3-6 months)
5. After the IV therapy is terminated, Remission with oral Drugs must be maintained with oral drugs for at least 2 years.
6. During the 3rd year Oral Therapy should be tapered off
7. After the 4th year without drug and without flare, Remission without Drug is achieved

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

Disease in Control was defined when after daily IV and oral therapy, and local injection, the CRP was < 3 mg/L and ESR was < 25 (< 15 mm in men/1 hour), the Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Metrology Index, Bath Ankylosing Patient Global Assessment Index are < 1, and Bath Ankylosing Spondylitis Functional Index < 2.

Remission with oral drugs was defined when the outcome of identical clinical Bath Ankylosing Spondylitis Scores, ESR, and CRP were maintained by daily oral therapy in similar status as in Disease in Control with Bath Ankylosing Spondylitis Radiology Index Scores not significantly worse after 2 years.

Remission without Drug is defined when the oral therapy is tapered off over a period of 1 year with another subsequent year without drug and flare with similar status retained as in Remission with oral Drugs.

Flare is defined when spinal and/or peripheral arthritis recur in ≥ 1 joint with Bath Ankylosing Spondylitis Disease Activity Index > 1 , abnormal levels of ESR and CRP.

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

How long does it takes to obtain Disease in Control in patients with NSAID-refractory AS?

2-4 months

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

5.5-7.5 months

How long does it takes to acquire Remission without Drugs?

53.5-55.5 years

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

Only Immunosuppressant-naïve patients with NSAIDS-refractory AS with BASRI < 2 can achieve Remission without Drug.

BASRI comprises Bath Ankylosing Spondylitis Radiology Spine or Bath Ankylosing Spondylitis Radiology Hip Index and is graded 0-4.

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

Immunosuppressant-naïve to SBP-6-IMNs is defined when the patient has never been exposed to treatment with IV Cyclophosphamide + Methylprednisolone + 5-Fluorouracil + weekly Methotrexate and oral Mycophenolate Mofetil + Cyclosporine. If any of the 6 drugs from the SBP-6-IMNs has been prescribed intermittently then the patient is not Immunosuppressant-naïve.

How long can Remission without Drug lasts in NSAID-refractory AS?

Remission without Drug can last long term or lifetime, provided early flare is immediately suppressed within the 1st week of onset by the SBP-6-IMNs.

In the medium term

Those patients who have been exposed to Immunosuppressants (not Immunosuppressant- naïve) with BASRI < 2 acquire Remission with oral Drugs

Those patients who are Immunosuppressant-naïve but with BASRI ≥ 2 erosions attain Remission with oral Drugs.

Those patients who have not been exposed to Immunosuppressants or Immunosuppressant- naïve with BASRI < 2 acquire Remission without Drug.

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

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

In the long-term

When required Remission with oral Drugs is sustained through long-term or lifetime by immediate suppression of early flare by the SBP-6-IMNs

Remission without Drug can be sustained long term or lifetime when any early flare is immediately suppressed by the SBP-6-IMNs.

Short term is defined for a period of < 5 years

Medium term is defined for a period of 5-10 years

Long term is defined for a period of > 10 years

What is the outcome of the treatment

In the short term

- Disease in Control
- Remission with oral Drugs
- Remission without Drug

In the medium term

- Maintenance of Remission with oral Drugs
- Sustaining Remission without Drug by suppression of early flares with the SBP-6-IMNs

In the long-term

- Maintenance of Remission with oral Drugs
- Sustaining Remission without Drug by immediate suppression of early flares with the SBP-6-IMNs

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

Anorexia, nausea, vomiting, gastric discomfort, and diarrheas are the gastrointestinal toxicities. Preceding IV infusion with Granisetron, H2 Antagonists and/or Proton Pump Inhibitor, antiemetic and spasmolytic, easily prevents these symptoms and signs.

What are the blood toxicities?

In the low dosages applied no blood toxicities are encountered. The blood toxicities could be leukopenia, cytopenia, and severe anemia or all three, which is called Pancytopenia.

What are the renal toxicities?

Copious fluid intake prior and after IV Cyclophosphamide prevent hemorrhagic cystitis. No renal toxicities are encountered due to the SBP-6-IMNs. Renal toxicities could be increase of serum creatinine of 30% within 1 year.

What are the liver toxicities?

In the low dosages applied no liver toxicities are encountered. Liver toxicities could be significant raise of SGPT and significant drop of serum Albumin.

What is the outcome of treatment of NSAID-refractory AS by the SBP-6-IMNs in the long term?

The first version applied in RF+ RA is the SBP-5-IMNs comprising IV Cyclophosphamide + Methylprednisolone + Methotrexate and oral Mycophenolate Mofetil + Cyclosporine. When IV 5-Fluorouracil is additional included, the treatment regimen becomes SBP-6-IMNs.

Radiological outcome of NSAID-refractory AS in a 6 years observational study:

BASRI < 2 and ≥ 2 becomes BASRI 0 and BASRI in status quo or not significantly worse compared with baseline*.

*John Darmawan, A Remy Nasution, Shun-le Chen, Syed Atiqul Haq Dongbao Zhao, Tran Thi Minh Hoa, Qingyu Zeng, Fereydoun Davatchi, Budi Liem. Six-years Outcome of NSAID-refractory Ankylosing Spondylitis after Treatment with the Step-down Bridge Protocol of Intravenous and Oral Combination of 5 Immunosuppressants. Submitted for review and publication.

Remission with oral Drugs was achieved in all Immunosuppressant-naïve NSAID-refractory Ankylosing Spondylitis with baseline BASRI ≥ 2 , except in 8.0% not immunosuppressant-naïve patients, who achieved 100% improvement of ASAS70. Remission without Drug was achieved in all Immunosuppressant-naïve NSAID-refractory Ankylosing Spondylitis with baseline BASRI grade < 2*.

Of the 79 patients 51.3% of the patients with Immunosuppressant-naïve BASRI ≥ 2 achieve Remission with oral Drugs and remain so in the medium term with early flares immediately suppressed by the

SBP-6-IMNs. The 40.2% of the patients with Immunosuppressant-naïve and BASRI < 2 acquires Remission without Drug and early flares are immediately suppressed by the SBP-6-IMNs in the medium term.

The 1.5% or 4 patients who are not Immunosuppressant-naïve but with BASRI ≥ 2 cannot achieve Disease in Control and Remission with oral Drugs. These 4 patients obtain improvements of ASAS70.

ASAS70 is another outcome measurement that is less demanding compared with Disease in Control, Remission with oral Drugs, and Remission without Drug

Not immunosuppressant-naïve patients have been exposed to intermittent high dosages of IV Cyclophosphamide of 800-1000 mg or 1000 mg of Methylprednisolone. However, they are still immunosuppressant-naïve to IV Methotrexate + 5-Fluorouracil and oral Mycophenolate Mofetil and Cyclosporine and achieve improvements of ASAS70.

Is Remission without Drug lasting long-term or lifetime a cure for NSAID-refractory AS?

Long term or lifetime Remission without Drug is no cure. The possibility of flares is real and requires immediately suppression by the SBP-6-IMNs to maintain Remission without Drug.

What happens when the patient dropped out during the treatment with the SBP-6-IMNs and return later for treatment again?

It is very likely that the NSAID-refractory flares in the mean time. However, the patient is not Immunosuppressant-naïve anymore when retreated with the SBP-6-IMNs. At the most retreatment with the SBP-6-IMNs achieve improvements of ASAS70. Remission without Drug is out of the question and Remission with oral Drugs is difficult to attain.

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

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

*Gladman DD, Urowitz MB, Rahman P, Ibanez D, Tam LS. Accrual of organ damage over time in patients with Systemic Lupus Erythematosus. J Rheumatol 2003 Sep;33(9):1955-1999.

These organ damages in Lupus Nephritis would occur in any other autoimmune diseases such as in NSAID-refractory AS.

Why are some patients with NSAID-refractory AS still prescribed Prednisone or Prednisolone or Methylprednisolone for long term or lifetime?

Dissemination of information in international scientific medical journals takes years even decades to spread over the world to the medical professionals. What has been standard therapy takes at least one generation of medical professionals to correct. In the mean time damage has been done and the consequences endured. This website is launched to communicate the newest and latest development in the treatment of autoimmune diseases such as Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Alzheimer's Disease besides the autoimmune rheumatic diseases.

The short, medium, and long term adverse effects of Prednisone, Prednisolone or Methylprednisolone are notorious and detrimental to the general health of the patients. These agents are used as a troubleshooter and Panacea when nothing helps. However, when it is used appropriately and adequately over a relative short period of time, it is very beneficial to the patient in controlling symptoms and signs of disease. That is why the SBP-6-IMNs contains intravenous Methylprednisolone for application in a relative short period of time.

ARE IV Cyclophosphamide adverse effects a risk factor for damage to the male and female fertility organs?

In high daily dosages and high total cumulative dose applied in the treatment of cancers, IV Cyclophosphamide may be associated with infertility and malignancy. It has been accepted that a total cumulative dose of maximum 3 g, the total number of IV sessions < 30 with < 100 mg of Cyclophosphamide per IV session, and the IV sessions spread over period of 7.5 months is safe.

The IV Cyclophosphamide and Methylprednisolone in NSAID-refractory Ankylosing Spondylitis

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

In the therapy of NSAID-refractory AS the total cumulative dose of the IV Cyclophosphamide from the SBP-6-IMNs is < 3 g, IV session is < 100 mg per dose, the frequency of IV session < 30 spread over a period of 7.5 months are within the safe limit for serious adverse effects. As adverse effects are IV and cumulative dose and time-exposure dependent, it is very unlikely that the SBP-6-IMNs will induce serious reactions. The initial 5X per week daily IV session although intensive, last only 1-2 months. With regard of Cyclophosphamide the SBP-6-IMNs is a safe treatment regimen.

What about the risk of short, medium, and long term adverse effects of 5-fluorouracil used in the SBP-6-IMNs?

5-Fluorouracil is given in IV and cumulative dosages, number of IV sessions, and period of exposure identical to Cyclophosphamide. Due to the different receptor sites for adverse effects, the patient is not collectively affected by Cyclophosphamide + 5-Fluorouracil together. Intravenous 5-Fluorouracil is as safe as IV Cyclophosphamide in the SBP-6-IMNs.

What about Methotrexate adverse effects?

Methotrexate has been applied in the therapy of Rheumatoid Arthritis (RA) about 4 decades ago. It is standard and classical therapy for RA in the Western countries. Its adverse effects and safety precautions to be taken when prescribing Methotrexate are well known. Biologic Response Modifiers are always applied in combination with Methotrexate in the treatment of NSAID-refractory AS. The Biologic Response Modifiers, Infiximab (Remicade), Etanercept (Enbrel), Adalimumab (Humira), Anakinra (Kinerett), and Rituximab (Mabthera) modify the response of NSAID-refractory AS to Methotrexate in the combination therapy.

What are the short, medium, and long term adverse effects of Mycophenolate Mofetil on the stomach?

The daily low dosages of Mycophenolate Mofetil of 500 mg bid/tid in the maintenance of Remission with oral Drugs in NSAID-refractory very rarely induce gastritis. The gastritis can be immediately overcome with proton pump inhibitors. Proton pump inhibitor taken before meals and the Mycophenolate Mofetil after meals can prevent flare of gastritis.

So far the mainstay of short, medium, and long term maintenance therapy in Remission with oral Drugs of NSAID-refractory AS is Mycophenolate Mofetil (Cellcept). Cyclosporine could be more locally irritating to the stomach compared with Mycophenolate Mofetil.

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

The therapeutic principle of the SBP-6-IMNs is to suppress the Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Metrology Index, Bath Ankylosing Spondylitis Patient Global Assessment Index to < 1, and Bath Ankylosing Spondylitis Functional Index < 2 and ESR from > 40 mm to < 20 mm/1 hour by the daily IV therapy of Cyclophosphamide + Methylprednisolone + 5-Fluorouracil and weekly Methotrexate. When the Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Metrology Index, Bath Ankylosing Spondylitis Patient Global Assessment Index is < 1, and Bath Ankylosing Spondylitis Functional Index < 2 and ESR < 20 mm, the daily oral therapy of

Mycophenolate Mofetil + Cyclosporine + weekly Methotrexate consolidate the Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Metrology Index, Bath Ankylosing Spondylitis Patient Global Assessment Index to < 1 , and Bath Ankylosing Spondylitis Functional Index < 2 and ESR < 20 mm for at least 2 years.

The misunderstanding is trying to suppress the Bath Ankylosing Spondylitis Disease Activity Index of > 4 and ESR > 40 mm by the oral therapy of the SBP-6-IMNs. The low dosages of the oral therapy within the limit of serious adverse effects are only effective when the ESR is normal and the Bath Ankylosing Spondylitis Disease Activity Index is < 1 .

Another misunderstanding is to equate the SBP-6-IMNs with chemotherapy for cancer treatment. The IV dosages of Cyclophosphamide + Methylprednisolone + 5-Fluorouracil and weekly Methotrexate are small compared with dosages of combination of cytostatics for treatment of cancer. As adverse effects of drugs are daily and cumulative dose dependent, the SBP-6-IMNs has safe low dosages with limited time exposure to IV Cyclophosphamide + Methylprednisolone + 5-Fluorouracil and weekly Methotrexate (see table above).