IMMUNO-SUPPRESSIVE THERAPY IN GLOMERULONEPHRITIS

P.J. Mahanta, S.C. Tiwari

Department of Nephrology AIIMS, Ansari Nagar, New Delhi-110029. India.

INTRODUCTION

Self tolerance means a state of absence of immune responsiveness to a self antigen. Self tolerance occurs due to two phenomena. *First* central tolerance is the process of the deletion of self reactive lymphocyte during maturation in bone marrow and thymus. *Second,* peripheral deletion, is the process of sequestration of self reactive T. cells that have escaped deletion in the thymus.

Auto-immune disease is believed to results from the bypass of at least one of the self tolerance mechanisms. The interaction between immunologic, genetic, environmental and even microbial factors play role in the initiation of this hazardous autoimmune response. Classsically, the immune system has been divided into two classes, humoral immunity, mediated by soluble antibody and cellular immunity, mediated by lymphocyte. Immune complex mediated glomerulonephritis is a classis humkoral response, whereas alteration in cellular response may responsible for the pathogenesis of minimal change disease. But there is evidence that in some diseases like ANCA associated glomerulonephitis, both d humoral and cell mediated immune response are involved.

Immuno-supressive medications, which are used for the treatment of various glomerulonephritis, may act by inhibiting or modifying different steps of immune response. It is important to remember that all immuno-suppressive medications are associated with serious adverse effect effect like, increased risk of infection and neoplasia. Therefore, in treating individual patient with glomerulonephritis, the risk versus benefits of the immunosuppressive medications must be weighed.

IMMUNOSUPPESSIVE AGENTS

Glucocorticoids; These have been used for may years as both immunosuppressive and anti-inflammatory agents. They suppress both cell mediated immunity, by inhibiting genes that code for important cytokines like Interleukin 1 through 6 and 8 and Interferon a, and humoral immunity, by diminishing B cell clonal expansion and antibody synthesis.

Currently, they are the most commonly used and are perhaps the most effective immunosuppressive medications for may only of the glomerular diseases either along or in combination with other drugs the cyclophophamide, azathioprine ormycophenolate. They are effective in minimal change disease(MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MGN), induction as well as maintenance therapy of lupusnephritis (LN) and rapidly progressive glomeulonephritis (RPGN)

As these agents are associated with many adverse effects, close monitoring is crucial. These adverse effects include an increase susceptibility to infection, impaired glucose tolerance, sodium retention, hypertension, osteoporosis, cataract, cushigoid appearance etc.

Azathiopine; has been used as an immunosuppressive agent since 1960. It is pro-drug, which is converted in the body to its active metabolite-6 mercaptopuine, which they act by inhibiting the formation of phosphoribosy 1 pyrophosphate, an intermediate in purine metabolism. The drug is now commonly used to treat lupus nephritis, lg A nephropathy, and severe proliferative glomerulonephritis such as ANCA associated glomerulonehritis as maintenance therapy, after induction with steroids and cyclophosphamide. It is used at the dose of 2 mg/kg/day. Azathioprine has generalble adverse effects. It causes acute myelo-suppression resulting in leucopenia, megaloblastic anemia, and thrombocytopenia, due to the incorporation of azathiopine derived 6-thiogunanine nucleotides into DNA. Other side effect includes nausea, vomiting, diarrhea and hepatotoxicity. Moreover, concomitant therapy with allopurino9l, which inhibits its metabolism, potentiates toxicity. Although previously believed to be safe in borne to pregnancy, recently few reports of leucopenia and thrombocytopenia in neonates mothers azathioprine during pregenancy.

Cyclophosphamide is a prodrug it is converted in the liver to the active metabolite 4-hydroxy cyclophosphamide and phosphoramide mustard. Then these bind to DNA and inhibit cell proliferation and results in dose dependent neutopenia and lymphopenia, with reduction of both B cell and CD4+ and CD8+ T cell.

Cyclophosphamide has been used to treat autoimmune glomerular diseases, both as an intravenous pulse and an oral form. For many years, it has been line D therapy for proliferative lupus nephritis and it remains the drug of choice for most patients with severe crescentic rapidly progressive glomerulonephritis, whether related to anti GBM antibody jor ANCA associated disease. It is also used to treat steroid resistant minimal change disease, FSSGS, Ig A nephropathy and membranous nephoroathy. As it is associated with significant adverse effects. The newer immunosuppressive like mycophenolate, is now becoming a popular alternative therapy. As induction thereapy, it is used as monthly intravenous pulse of 0.5 to 1.0 g/m2 or daily oral cyclophosphanide 2 mg/kg/for about 6 months.

Cyclophosphamids causes dose dependant bone marrow suppression, and may results in anemia, leucopenia or thrombocytopenia. The effect on leukocyte is most pronounced, the aim should be to keep the TLC above 3000/cmm and cumulative dose should not exceed more than 200 mg/kg. Infections are especially common in neutropenic patient, but major bacterial and fungal infections can occur even without neutropenia, especially in the presence of concomitant steroid therapy

Small amount of cyclophosphamide metabolite may convert to acrolein, which is toxic tobladder epithelium, leading to hemorrhagic cystitis. It is usually are with intravenous route and aggressive hydration may prevent this complication. It can leads to infertility in both male and females, and it should not be given to pregnant women, unless absolutely indicated, because of treatogenicity.

Other side effects are nausea, hair loss, mouth sores, hyponaturemia due to increased released of antidiuretic hormones and long terms risk of malignancy. Because of these major toxicities, a strategy that should be strongly considered is induction therapy with cyclophophemide, and then maintenance therapy with a less toxic drug like mycophenolate or azathioprine.

Correspondence: Prof. S. C. Tiwari, *Fax: 91-11-26588641,* ***e-mail:*** *sctiwari@hotmail.com*

Chlorambucil is also a nitrogen mustard alkylating agent. Its mechanism of action is similar to cyclophophamide. It has been used to treat steroid resistant minimal change disease, FSGS, and membransousnephropathy, as a part of alternating monthly regime with steroid. The commonly used dose is 0.12 mg/kg/day. Major adverse effects include bone marrow suppression, CNS toxicity hepato toxicity, infertility, strong teratogenicity and delayed malignancy.

Cyclosporin is a peptide derived from the soil fungusTolypocladium inflatum . In 1970, cyclosporine was introduced as an anti-rejection agent for organ transplantation. Cyclosporin is a calcineurin inhibitor that suppresses the immune response by down-regulating the transcription of various cytokine genes, mainly interleukin-2 (IL-2), which serves as the major activation factorfor T-cells in numerous immunological processes. A further effect of IL-2 inhibition is a reduction in B-cells activation and subsequent antibody production, IL-2 level increase during proteinuria, and normalize during remission in adults with the INS and in children with MCD or FSGS. This may be a part of a generalized disorder of cellular immunity that results in nephritic syndrome, rather than being causal of proteinuria. Cyclosporin may also have an anti-proteinuric action through its effect on glomerular permeability.

Cyclosporin has significant nephrotoxicity. Studies have demonstrated that at least in the acute situation these changes are functional and are promptly reversed following dose reduction or cessation of therapy. A current recommendation is the reduction of cyclosporine dose if serum creatinine increases by -30% above the patient's baseline value (even if this increase is within the normal range).

The clinical efficacy and safety of once a day and pre-prandial administration of cyclosporine in patients with idiopathic nephrotic syndrome is currently being investigated. Cyclosporin is an effective treatment for minimal change disease, FAGS, and membranous nephropathy. It is also effective in adjunct to steroid in class V (membranous) lupus nephritis. Recent Grade A evidence supports its use after a 12-week course of cytotoxic therapy, that has failed in steroid dependant or ssteroid resistant MCD and as a first-line option in MGN and FSGS either as monotherapy or in combination with corticosteroids. Cyclosporin therapy provides a sustained remission of proteinuria in a significant proportion of patients. The side-effect profile of cyclosporine is well known and predictable. Adherence to dosing guidelines plus regular patient monitoring will minimize the risk of nephrotoxicity.

In children, cyclosporine should be started at 100mg/m2/day and may be increased to 150 mg/m2/day. In adult, the dose is 2mg/kg/day and gradually increased at 2-week intervals until remission is achieved. The maximum dose is 5 mg/kg/day.

Treatment target include complete or partial remission of proteinuria, preservation of stable GFR (+-20% of pretreatment level), and a C0 cyclosporin level of 80-175 ng/ml. In the steroid-resistant or dependent cases following complete remission of proteinuria, cyclosporine should be continued for 1-4 years and then tapered gradually to lowest effective does.

Children continuing on long-term cyclosporine therapy should be regularly monitored, including a renal biopsy every 2-3 years to cheek for histological evidence of nephrotoxicity. Adults continuing on long-term cyclosporine therapy should also be regularly monitored, including a repeat renal biopsy at 12-24 months, especiallyifserum creatinine is -30% above the baseline level, and/or if the maintenance dose of cyclosporine require is -3.5mg/kg/day. In those, who are non –responsive to corticosteroids, cyclosporine should be given for at least 6 months before declaring it as treatment failure. Repeat biopsies should be carried out in a patient of FSGS with rapidly declining renal function, a marked disparity between an increasing serum creatinine and decreasing proteinuria and in patients receiving cyclosporine therapy beyond 2-3 years. The presence of increasing fibrosis and tubular interstitial disease should lead to a careful review of the case. It is often difficult to differentiate between drug toxicity and the natural history of the FSGS disease and hence the decision between lowering or discontinuing medication and/or adding adjunctive therapy remains a balance between the patient's clinical course/response or the observed histologic changes. Renal function (GFR) serves as a guide more than renal histology.

Tacrolimus is another calcineurin inhibitor, which binds to an immunophilin, FK binding protein -12. Then this complex interacts and inhibits calcineuin, resulting in actions similar to cyclosporine, Like cyclosporine, it is also nephrotoxic, and has similar toxicity profile. Recently tacolimus is also tried in few RCT as a monotherapy in membranous nephropathy, with promising results. The acrolimus target trough was 5 jto 8 ng/ml in that study.

Mycophenolate mofetil (MMF) , a prodrug of mycophenolic acid, is an immuno-suppressive agent that blocks purine biosynthesis by inhibiting the enzyme inosine monophosphate dehydrogenase (IMPDH). MMF inhibits T-and B-lymphocyte proliferation, induces apoptosis of activated T-lymphocytes, reduces synthesis of antibodies and may decrease the migration of inflammatory cells into glomeruli after antibody deposition. It also prevents glomerular injury, prevents progressive renal scarring and fibrosis by inhibiting mesangial cell proliferation. MMF does not induce nephrotoxicity and is relatively well tolerated.

MMF has been shown to be effective in several induction and maintenance studies of severe lupus nephritis. It is now being studied in FSGS, lg A nephropathy, membranous nephropathy, steroid resistant nephritic syndrome and as maintenance therapy for ANCA associated glomerulonphritis.

Most common adverse effects or MMF are gastrointestinal upset including nausea, abdominal pain and diarrhea, which can be reduced by dividing the total dose. Other adverse effects are leucopenia, which responds to dose reduction and increased risk of infection. Available data suggest that MMF is better than AZA in kidney transplantation and a good, but not necessarily a better alternative to AZA in lupus nephritis.

As an induction therapy in class IV lupus nephritis, most of the studies have used MMF at the dose of 2.0 – 3.0 g/day for 6 months or more, along with prednisone 1 mg/kg/day. As a maintenance therapy, the dose of MMF is 1.0 -2.0 g/day, along with alternate day prednisone (0.25 mg/day). For therapy in FSGS, Ig A nephropathy, membranous nephropathy, steroid resistant nephritic syndrome and as maintenance therapy for ANCA associated glomerulonaphritis, MMF has been used at the dose of 1.0 -2.0 g/day, along with or after remission achieved by steroid, and with highest tolerated dose of ACEI or ARB, for a duration of 12 months or more. The target CO-MPA blood level was between 1.5 and 4.5 mg/ml.

Sirolimus, is ja macrolide antibiotic, and like tacrolimus binds to immunophilin FK binding protein 12. Then this complex binds to mTOR, there by inhibit cell cycle, through blockage of GI to S phase transition, resulting in inhibition of growth of haematopoitic and lymphoid cells (T cells). It is approved for use in organ transplantation by FDA in 1999. As it has antiproliferative and immunosuppressive action, it has been tried in few trials of steroid resistant FSGS withvariable results.

Unlike calcineurin inhibitors, it is not nephrotoxic, reported adverse effects are impaired wound healing, hyperlipidaemia, reversible

cytopensias, and inceased susceptibility to infection.

Rituximab a monoclonal antibody (mAb) against the CD20 antigen present on B clles, was approved by the FDA in 1997 for the treatment of relapsed or refractory non-Hodgkin's lymphoma and more recently for patients with RA. Because the CD20 antigen is not expressed on hematopoietic stem cells, normal plasma cells, or other normal tissues, the use of this mAb allows for selective depletion of B cells.

In nephrology, it is being actively evaluated as an immuno-modulator in lupus nephritis, Wegener's granulomatosis, ANCA associated rapaidly progressive glmerulonephritis, membranous nephropathy, few cases of steroid resistant minimal change disease and FSGS. Recommended dose is four weekly doses of 375mg/m2 or 2 doses 1000 mg given two weeks apart.

Reported adverse effects are allergic reactions, hypotension, reactivation of viral infections like HBV, JC virus and progressive multi focal leukoencehalopathy.

Mizoribine is an immunosuppressive agent and has been used in Japan for the treatment of lupus nephrities, glomerulonephritis, transplant rejection and rheumatoid arthritis. Its active form mizoribine -5-P, selectively inhibits inosine monophosphate and guanosine monophosphatase synthetase, resulting in blockage of guanosine synthesis, which leads to inhibition of activation and proliferation of T cell.

It has reported to be safer than other conventional immunosuppressive medications and reported adverse effects are hyperuricaemia with use of high dose and rhabdomyolysis with concomitant use with statins.

Intravenous immunoglobulin has variety of immunomidulatory action, including acceleration of catabolism of Ig G. They have been tried in diseases like lupus nephritis, henoch-schonlein purpura, and number of glomerulonephritis, with variable results.

As they possess a number of side effects including acute renal failure, especially seen with sucrose based IV IG, they should be cautiously used until their precise role has been established.

CONCLUSION:

The primary glomerular diseases are a type of immuno – inflammation having various types of immune reactions (acute and chronic BSA mode). The purpose of using immuno-inflammatory therapy is to decrease the degree of proteinuria and to decrease the ongoing immuno-inflammation. The choice of drug should be such that it decreses the degree of drug should be such that itdecrease proteinuria and immuno-inflammation, as well as has minimal possible and reversible adverse effects. The Hence the physician and the nephrologists should use the appropriate drug and doses, and should carefully monitor the foradverse effect profile.

RECOMMENDED READING

1. *Cattran et al Cyclosporin in idiopathic glomerular disease associated with the nephritic syndrome: Workshop recommendations,. Kidney International (2007) 72,1429-1447.*
2. *Praga M, Barrio, V, Fernandez-Juarez, G Luno J. Tarcolimus monotherapy in membranous nephropathy; a randomized controlled trial. Kidney Int 2007; 71: 924-930.*
3. *Sepe et al,Mycophenolate mofetil in primary glomerulopathies Kidney International (2008) 73, 154-162.*
4. *Rituximab treatment of idiopathic membranous nephropathy, Fervenza et al, Kindney International (2008) 73,117-125*
5. *Sepe et al, Inferferon-B Reduces Proteinuria in Experimental Glomerulonephritis; J Am Soc Nephrol 18;2875-2884, 2007.*
6. *Brenner and Rector's – The Kidney, 8th edition.*
7. *Diseases of the kidney & urinary tract, R.W. Schrier, 8th edition.*
8. *Therapy in Nephrology and Hypertension, C.S. Wilcox, 3rd edition.*

Conference News

World Congress on Clinical, Preventive and Geriatric Cardiology (WCCPGC 2009)

October 2nd to 4th, 2009

At Swaminarayan Akshardham, N.H. 24, Akshardham Setu, Near Noida, New Delhi- 92, India

Organisers: WHA, AACIO, CSI DB, APSC, CAPSC, SA, IMSA, ISCU, IAE, DRDO, CHC, EI, WAMS, WASS, WAMBM & BSC

Host: Swaminarayan Akshardham, New Delhi, 110092

Partners: Media Partners: Times Foundation, Nai Duniya, Express Healthcare, Corporate Partner: ASSOCHAM, PSUs Partner: SCOPE,

Electronic Media Partner: NDTV, Knowledge Partner: PriceWaterhouse Coopers (PWC), Health Magazine; Life positive; Heal India

H.K. Chopra	***S. K. Parashar***	***Navin C. Nanda***	***Anil Kumar***	***Rakesh Gupta***	***Satish Kr. Gupta***	***Rajeev Gupta***
Chairman	*Chairman,*	*International*	*Chairman*	*Chairman*	*Secretary*	***D. Prabhakaran***
Organizing	*Scientific*	*President*	*Reception*	*Coordination*	*General*	*Convenors*

Her Excellency Mrs. Pratibha Patil, Hon.ble President of India has been requested to be the Chief Guest.

Faculty: National and International of Repute

SCIENTIFIC HIGHLIGHTS (WCCPGC 2009)

Recent advances in clinical cardiology, preventive cardiology, hypertension, congestive heart failure, dyslipidemia, coronary artery disease, medical angioplasty, coronary imaging, cardiodiabetes, metabolic syndrome, echocardiography, electrophysiology and cardiac arrhythmia, interventional cardiology, cardiovascular surgery and cardiac anesthesia etc.

"Kindly confirm your participation"."Registration and local hospitality is free" on "first come first serve Basis up to Sept. 1st, 2009"

For Registration:

Dr. H.K. Chopra,
Organising Chairman,WCCPGC-2009
C/o IMSA World HQ,
2nd Floor National Medical Library, Ansari Nagar, New Delhi – 110029
E-mail: drhkchopra@yahoo.com
Fax: 91-11-26444242, M: +91-9811090204
Ph: 91-11-26444242, 25658826, 26656990

Ms. Surbhi Bhuddi
Manager, WCCPGC-2009
CHC, No.5A/11041, 3rd Floor, W.E.A, Karol Bagh, New Delhi 110005 - India
E-mail:- surbhi@cardiopulseheartcare.com
Fax: 91-11-25815540, M: +91-9212596645
Ph: +91-11-25815539 Extn. 33
All India Toll Free No; 1800 11 33 22

Website : www.wccpgc.com