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INTRAVENOUS IMMUNOGLOBULIN THERAPY IN THE TREATMENT OF IDIOPATHIC THROMBOCYTOPAENIC PURPURA

Idiopathic thrombocytopaenic purpura (ITP) is a disease characterised by a severe reduction in the number of platelets in the peripheral blood. In most cases, there is an autoimmune antibody mediated process leading to the destruction of platelets, the antibody being of IgG type. The demonstration of the antibody is often not possible. The main presenting features include purpura and bleeding from mucous membranes, haematuria, haematemesis and melaena. Intracranial haemorrhage is the most serious complication that may occur, which is heralded by headache, dizziness and confusion.

Diagnosis of the disease is established by finding severe thrombocytopaenia with normal or increased numbers of megakaryocytes in the bone marrow. Steroids, immunosuppressive drugs or splenectomy usually induce lasting remission, but some patients remain refractory to each of these treatment modalities.

Ever since the initial report¹ in 1981, of the rapid reversal of acute and chronic thrombocytopaenia in children by high dose intravenous immunoglobulin (IVIG), numerous reports have appeared in literature regarding its effectiveness in the treatment of ITP. However, being a relatively new therapy, many aspects of IVIG therapy are still not clearly understood. Further, the efficacy of this mode of treatment is still not confirmed as conflicting reports have appeared in

literature²⁻⁴. Available data on the choice of patients, effectiveness of therapy and mechanism of action of IgG have been reviewed in the present write-up.

Characteristics of ITP

ITP is usually associated with the occurrence of platelet antibodies (auto- or allo-immune type and/or of platelet bound complement (C3))¹, and is characterized by low platelet count ($<30 \times 10^9/l$), bleeding disorders and perhaps by rash and petechiae. A lowered platelet count is the result of sequestration and lysis of antibody sensitized platelets by cells of the reticuloendothelial system either in the spleen or liver⁵. Circulating immune complexes may also be present⁶. Another feature of ITP is increased megakaryopoiesis in the bone marrow of most patients.

The acute form of ITP which is more common in children usually occurs after viral infection and responds to conventional treatment. The chronic form, more frequently found in adults, is generally of autoimmune type and sometimes resistant to all forms of treatment. It has a female : male ratio of 2:1—4:1⁷.

Indication for IVIG Therapy

Steroids, immunosuppressives and splenectomy are the usual modes of treatment. Recently the use of danazol, an androgenic preparation has been advocated^{8,9}.

However, some patients particularly of chronic ITP do not respond to conventional treatment. Moreover, the long-term usage of steroids and cytotoxic drugs is not without serious risks¹⁰. If a bleeding crisis is precipitated, with the danger of intracranial haemorrhage pre- or post-operatively or when a patient refractory to steroids is to be prepared for surgery, one may opt for IVIG therapy^{2,4}, in such situations.

Choice of Patients

Both children and adults with chronic/acute ITP have been subjected to IVIG therapy^{1,4}. Elderly patients above 60 years of age, were also subjected to this treatment though with not much success¹¹. Patients with chronic autoimmune thrombocytopaenic purpura associated with other diseases such as HIV carriage, NHL, cancer and Wiskott-Aldrich syndrome were also given IVIG with success^{1,4,12}. Pregnant women with ITP have also been treated with IVIG¹³.

IVIG Preparations

IgG is prepared from pooled human plasma usually by the classical Cohn's fractionation method¹⁴. Fraction II which consists mainly of IgG is generally used. Titres of IgA and IgM antibodies are maintained below 1:16 to avoid complications similar to transfusion¹⁵. IgG aggregates which can cause severe anaphylactic reactions in recipients are also removed by one of several methods available¹⁶.

Most IVIG preparations are monomeric with intact recognition and effector functions. the subclass distribution, function and biological half-life of these products are very similar to normal serum IgG.

Mode of Treatment

A dose of 0.4 g/kg body wt/day to be administered *iv* for 5 days has been advocated^{1,3} but higher doses upto 2.4 g/kg body wt have also been administered in patients who do not respond to low doses¹². Maintenance doses, if necessary consisted of 0.4 g/kg body wt every 1-6 weeks¹.

Supplementary therapy of steroids, immunosuppressives¹ and splenectomy associated with IVIG infusion has been reported⁴.

Response to Treatment

Clinical

Following IVIG administration, a significant increase in platelet count has been reported in acute as well as chronic ITP in adults^{2,4,12,19} including pregnant women¹³, and children^{1,19}. There was a decrease in

platelet bound immunoglobulin and complement^{4,20,21}. In general, children responded better particularly those with acute ITP and long-term response was also better in them^{3,16}.

Bussel and Pham¹⁸ who reviewed the literature on chronic adult ITP treated with IVIG, reported that unmodified immunoglobulin was better than modified one. Greater percentage of patients were refractory among those who had ITP for more than 3 years prior to IVIG treatment. A higher peak platelet count immediately after IVIG infusion was correlated with a longer duration of platelet response. Female patients respond better to IVIG than males. Patients above 60 years of age showed weaker responses than the younger ones. Splenectomized patients following IVIG fared better^{4,18}. Non responders included certain patients with aplastic anaemia or haemolytic anaemia and adult patients of chronic ITP¹.

IgG therapy did not interfere with other treatments and patients with malignancies continued either with radiotherapy or chemotherapy⁴.

Platelet function tests

Platelet function was mostly restored to normal as measured by bleeding and clotting time². Platelet aggregation tests employing ADP, collagen, adrenaline and ristocetin on platelet rich plasma were found to be normal in most responders^{2,4}.

Correlation between platelet antibodies and IVIG therapy

There was no correlation between the presence of autoantibodies and the Ig class of antibody and pattern of response to infusion⁴. IgG and IgM antibodies were detected though combination of IgM and IgG were also found⁴. In certain patients an inverse relation was observed between antibody on platelets and success of IgG therapy^{2,19}. Individuals with autoantibodies had better recovery than those with alloantibodies²¹. In a patient who was a non-responder, there was a five-fold increase in platelet antibodies after infusion⁴.

Serum immunoglobulin levels

Serum IgG levels showed a significant increase^{1,4,19} after treatment. IgA levels remained unaltered while reports about IgM levels are contradictory^{3,4}.

Adverse Effects of IVIG Therapy

The usual anaphylactic reactions were not observed in most patients^{1,3} though a few patients experienced chills, headache, fever and nausea^{4,12}. Wooduff *et al*¹¹ reported association between fatal thrombotic event

and IgG therapy in patients older than 60 years with atherosclerotic disease especially if the infused IVIG possessed the agonist properties. Development of non-A non-B hepatitis in several patients and haemolytic anaemia in one patient¹⁵ has been documented after IVIG therapy.

Mechanism of Action of IVIG

Many hypotheses have been put forward for the mechanism of action of IVIG. These include blockade of Fc (IgG) receptors of macrophages, decreased synthesis of antibodies and interference with the binding of platelet specific antibodies to the target antigen.

Several workers^{2,4,14} have concluded that immediate response to IVIG therapy may be due to transient blockade of IgG-Fc receptors on the macrophages of the reticuloendothelial system. Competitive binding and saturation by erythrocytes coated with IgG derived from the infusion together with the sensitized platelets affect the blockade of Fc receptors on macrophages²³. A role of low affinity Fc receptors in ITP has also been shown²⁴.

According to Hassig¹⁶ the beneficial effect of IVIG seen in children with acute ITP was probably due to repletion of a selective deficiency of antibodies specific for viral epitopes, since acute ITP at least in children, was almost always the result of inefficient immune response to a virus infection.

Some workers have suggested that high dose gammaglobulin was immunomodulatory *in vivo* either by alteration of the anti-idiotypic network or modulation of suppressor T-lymphocytes, thereby leading to depressed immunoglobulin production including the production of any platelet specific antibodies^{25,26}. Others have suggested that high dose gammaglobulin may directly interfere with the binding of platelet specific antibodies to the target antigens²⁰.

However, Barbano *et al*¹⁹ did not find any evidence for a decrease in platelet specific antibodies in both the adult and pediatric ITP patients undergoing an acute response to therapy and have supported the Fc blockade hypothesis for the short-term effect of high dose gammaglobulin.

The guidelines for the proper use of IVIG therapy have been provided²⁷ in the WHO report of 1983.

At present, IgG therapy is expensive. However, with simpler automated methods of plasma fractionation IVIG therapy will be more cost effective and put to widespread use.

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This write-up is based on an article entitled "Intravenous immunoglobulin therapy- An alternate approach in the treatment of idiopathic thrombocytopenic purpura", by P. Sharma, published in Immunohaematology Bulletin, 19(2)-1988.

ABSTRACTS

Some Projects completed Recently

B Cell alloantigen markers in patients with rheumatic fever and rheumatic heart disease.

The study was undertaken on 208 patients of rheumatic heart disease (RHD) of both sexes and 156 matched controls representing north Indian population to clarify the role of genetic susceptibility to rheumatic fever (RF)/RHD following streptococcal pharyngitis. Of the 208 RHD patients, 60 were typed for 883⁺ alloantigen, 50 for 256⁺ alloantigen and 98 for D 8/17 alloantigen. Out of 156 controls 50, 50 and 56 individuals were typed for 883⁺, 256⁺ and D 8/17 alloantigens respectively.

Frequencies of B cell alloantigens 883⁺ and 256⁺ were found to be 66.6 per cent (40 of 60) and 20 per cent (10 of 50) respectively in RHD patients as compared to 12 per cent (6 of 50) and 8 per cent (4 of 50) respectively in controls. Sixty three (64.2%) of the 98 RHD patients were positive for alloantigen D8/17 as compared to 10.7

per cent (6 of 56) of the controls. Positivity for D8/17 alloantigen increased with age, both in RHD patients and controls, upto the fifth decade, thereafter it declined.

Of the three B cell alloantigens, the high predictive value of genetic markers 883⁺ and D8/17 is of interest and provides evidence for the value of B cell alloantigens as genetic determinants for disease associations. This study revealed that the relative risk of developing RF and subsequently RHD in north Indian individuals bearing D 8/17 marker is approximately 9 per cent of the normal population.

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Role of mycobacterial RNA in immunoprophylaxis of experimental tuberculosis.

The present investigation was carried out to examine the role and mechanism of action of RNA isolated from *Mycobacterium tuberculosis* H₃₇Ra and its different fractions in inducing immune responses (both humoral and cell mediated), as also antituberculous protection.

Whole mycobacterial RNA was isolated with low protein and DNA as contaminants; the ratio of protein and RNA and DNA and RNA being 1:7.19 and 1:67.72 respectively. RNA was fractioned over sepharose CL-4/B and out of 3 fractions (F₁, F₂ and F₃) F₁ constituted the major part of the RNA. F₁ and F₂ fractions had comparable immunoreactivity while that of F₃ was low.

Mycobacterial RNA was complexed with Freund's incomplete adjuvant (FIA) in the ratio of 1:3 and administered to mice at the dose of 150 µg per mouse. RNA-FIA complexes elicited weak humoral response which could only be detected by ELISA. But a

significantly higher titre ($P < 0.01$) of RNA antibodies could be detected during the second weak post immunization. However, significant cellular immune responses were observed which were directed specifically against mycobacterial RNA. Immunized mice exhibited a significant level of protection against challenge with LD₅₀ dose of *M. tuberculosis* H₃₇Rv on the basis of per cent survival, lung density, root specific lung weight and viable counts in different organs. The protection induced by RNA-FIA complex was comparable to that of BCG, except that BCG vaccinated mice revealed a greater decrease or clearance of bacterial load. Further, protection was found to be mediated by immunocompetent T-cells, while the role of immune sera in imparting protection was minimal.

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ICMR NEWS

The following meetings of various Scientific Advisory Committees/Expert Groups/Project Review Committees/Scientific Advisory Groups/Task Forces of the Council were held during the month:

Meetings of the Scientific Advisory Committees (SACs) of the Permanent Institutes/Centres:

SAC of the Institute for Research in Reproduction, August 21-22, 1989 (at Bombay) Bombay.

SAC of the ICMR Genetic Medical Research Centre, August 22, 1989 (at Bombay) Bombay.

Meetings of the Expert Groups (EGs)/Project Review Committee (PRC)/Task Force (TF)/Scientific Advisory Groups (SAGs), held at New Delhi:

EG on Longitudinal Study of Haematological and Clinical Profile of People Infected with AIDS Virus. August 7, 1989

PRC on Virology and HIV Infection. August 8, 1989

EG on Indian Journal of Medical Research. August 8, 1989

TF on Venoms and Toxins August 9, 1989

SAG of the Division of Non-Communicable Diseases. August 28-29, 1989

SAG of the Division of Human Resources Development Research. August 30-31, 1989

Participation of ICMR Scientists in Scientific Events:

Dr. B. Ravindran, Senior Research Officer, Regional Medical Research Centre, Bhubaneswar and Dr. M.M. Mehta, Research Officer, Institute of Immunohaematology, Bombay, participated in the VII International Congress of Immunology, at West Berlin (July 30 to August 5, 1989).

Dr. B.K. Tyagi, Senior Research Officer, Desert Medicine Research Centre, Jodhpur, participated in the X International Symposium of Odonatology, at Johnson City, USA (August 6-12, 1989).

Dr. A.S. Paintal, Director-General, ICMR, delivered the eighth Prof. V. Ramakrishna Memorial Lecture on "Evaluation of Work by Scientists", at the Indian Institute of Technology, New Delhi (August 10, 1989).

Dr. Mehtab S. Bamji, Director Grade Scientist, National Institute of Nutrition, Hyderabad, participated in the V International Congress of the Federation of Asian and Oceanian Biochemists, at Seoul (August 13-18, 1989). She also participated in a symposium on New

Trends in Biological Chemistry, at Nagoya, Japan (August 22-23, 1989).

Five Scientists of National Institute of Nutrition, Hyderabad, viz Dr. Vinodini Reddy, Director; Dr. K. Krishnaswamy, Dy. Director; Dr. Gafoorunissa and Dr. K. Satyanarayana, Asstt. Directors; and Dr. V. Jagadeesan, Sr. Research Officer, participated in the XIV International Congress of Nutrition, at Seoul (August 20-25, 1989).

Sh. B. Bhattacharya, Financial Adviser, ICMR, relinquished his charge to take over as Joint Secretary (Finance), Ministry of Urban Development on August 11, 1989. On the same day Sh. P.B. Saxena took over as the Financial Adviser of the ICMR.

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The Council's Desert Medicine Research Centre at Jodhpur has been renamed as Regional Medical Research Centre.

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
National Conference on Recent Trends in Physical Chemistry.	August 2-3, 1989; Calcutta	Dr. R.V. Gopala Rao, Department of Chemistry, Jadavpur University, Calcutta.
Continuing Medical Education Programme on Rheumatology Update.	August 12-13, 1989; Hyderabad	Dr. Kakarla Subbarao, Director, The Nizam's Institute of Medical Sciences, Hyderabad.
VII IMA/CGP National Conference on General Practice.	August 18-20, 1989; Varanasi	Dr. S.P. Gupta, Organising Secretary, 7th IMA/CGP National Conference, IMA House, 7/31, Chetganj, Varanasi.
National Seminar on Strategies for Optimal Management of Cancer in Developing Countries.	August 24-27, 1989; Srinagar	Dr. Shad S. Akhter, Department of Medical Oncology, Sher-I-Kashmir Institute of Medical Sciences, Srinagar.
V National Conference on Aerobiology.	August 28 to September, I, 1989; Srinagar	Dr. A.H. Munshi, Department of Botany, University of Kashmir, Srinagar.
National Seminar on Newer Challenges in Medicine.	September 9-10, 1989; Jabalpur	Dr. B.N. Shrivastava, Professor & Head, Department of Medicine, and Dean, Medical College, Jabalpur, Jabalpur.
Symposium on Early Breast Cancer, and Workshops on Laser in Cancer Surgery; and Epidemiology of oral cancer.	September 9-10, 1989; Indore	Dr. S.K. Shukla, Organizing Secretary, VI National Cancer Convention, M.G.M. Medical College, Indore.
XV Mid Term Conference of Indian Association of Paediatric Surgeons.	September 28-30, 1989; Srinagar	Dr. Mahmooda Khan, Professor & Head, Department of Surgery, Government Medical College, Srinagar.
Seminar on New Trends in Methodology for Social and Population Research.	October 1-3, 1989; Tirupati	Prof. K. Mahadevan, Department of Population Studies, S.V. University, Tirupati.
National Workshop on Burns Injuries and their Sequele.	October 7-8, 1989; Chandigarh	Dr. C.P. Sawhney, Professor & Head, Department of Plastic Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh.
XVI Annual Conference of Indian Immunology Society and Symposium on Tropical Immunology.	October 12-14, 1989; Sevagram	Dr. B.C. Harinath, Professor & Head, Department of Biochemistry, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha.
Symposium on Reproductive Biology and Fertility Control.	October 12-14, 1989; Imphal	Dr. B.K. Omar, Professor & Head, Department of Anatomy, and Secretary, Anatomical Society of India, Regional Medical College, Imphal.
Symposium on Respiratory Allergy and Applied Immunology.	October 14-16, 1989; Hyderabad	Dr. M. Sundaramma, Professor & Chest Physician, Osmania Medical College and A.P. Chest Hospital, Hyderabad.
XXII Annual Convention of the Indian Dietetic Association.	October 19-20, 1989; Hyderabad	Dr. Indira Ray, Reader, Home & Social Science Department, Calcutta University, Calcutta.

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
Brachytherapy Workshop for Cancer Cervix.	November, 1989; Betul (M.P.)	Dr. Anand Vijay Kumar, Secretary, Paramedical Section, Christian Medical Association of India, Smruti Theatre Compound, Nagpur.
All India Symposium on Biophysics of Cell Structure and Function.	November 6-8, 1989; Chandigarh	Dr. P.C. Mangal, Chairman, Department of Bio-Physics, Punjab University, Chandigarh.
Seminar on Zoonoses.	November 9-10, 1989; Dibrugarh	Dr. L.P. Datta, Director, Regional Medical Research Centre (ICMR), P.B. No.105, Dibrugarh.
XVI Biennial Conference of the Indian Association of Leprologists.	November 9-12, 1989; Trichur	Dr. P. Vijay Shanker, Damien Institute, Ayyappankavu, Trichur.
Seminar on Pathology of Cardiomyopathies.	November 11, 1989; Bhubaneswar	Professor L.N. Mohapatra, Convenor, Indian Association of Pathologists and Microbiologists (Orissa Chapter) and Director, Regional Medical Research Centre (ICMR), Bhubaneswar.
Conference on Health Care for the Villagers and Urban Slums.	November 23-25, 1989; Calcutta	Dr. Ashok Sahani, Professor & Hony. Executive Director, Indian Society of Health Administrators, 104 (13/37), Cambridge Road Cross, Ulsoor, Bangalore.
National Seminar on Squint and Amblyopia.	November 25-27, 1989; New Delhi	Dr. Vimla Menon, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi.
All India Symposium on Reproductive Biology and General Endocrinology.	November 26-28, 1989; Baroda	Prof. P.M. Ambedkar, Department of Zoology, M.S. University of Baroda, Baroda.
Workshop on Recent Advances in Intensive Care.	November 26-30, 1989; New Delhi	Dr. H.K. Kaul, Professor & Head, Department of Anaesthesiology, All India Institute of Medical Sciences, New Delhi.
XXXIII All India Obstetric and Gynaecological Congress.	December 28-30, 1989; Patna	Dr. J. Mishra, Department of Obstetrics and Gynaecology, Hospital for Women, Patna Medical College Hospital, Patna.
Seminar on Indian Speech, Language and Hearing Tests - the proposed ISHA battery.	February 8-9, 1990; New Delhi	Dr. S.K. Kacker, Professor & Head, Department of Otorhinolaryngology, All India Institute of Medical Sciences, New Delhi.

COUNCIL'S TRAINING PROGRAMMES

Leprosy

At the Central Jalma Institute for Leprosy, Agra:

- ... Training Course on Leprosy for Medical Officers (August/September, 1989).

Virology

At the National Institute of Virology, Pune:

- ... Short-term Course on Detection and Isolation of Arboviruses Using Mosquito Inoculation and Mosquito Cell Culture (October, 1989).

Endocrinology

At the National Institute of Nutrition, Hyderabad:

- ... Annual Training Course on Endocrinological Techniques and their Application (August/September, 1989).

Nutrition

At the National Institute of Nutrition, Hyderabad:

- ... Annual Certificate Course in Nutrition (December 1, 1989 to February 28, 1990).

Occupational Health

At the National Institute of Occupational Health, Ahmedabad:

- ... Refresher Course for Industrial/ESIS Medical Officers (October 9-14, 1989).
- ... Training Course on Disaster Management of Hazardous Chemicals in Industry for Industrial Physicians, Chemists, Safety Officers, Hygienists (November 6-10, 1989).

Cytology

At the Institute of Cytology and Preventive Oncology, New Delhi:

- ... Indo-US Workshop on Chemoprevention of the Uterine Cervical Dysplasia with Nutrient Intervention (December, 1989).

Haematology

At the Institute of Immunohaematology, Bombay:

- ... Training Course in Blood Banking Technology and Immunohaematology for Medical Officers (August 1 to September 30, 1989).

Laboratory Animal Technology

At the Laboratory Animal Information Service Centre, National Institute of Nutrition, Hyderabad:

- ... Training Course for Laboratory Animal Supervisors (September 1 to November 30, 1989).

Clinical Pharmacology

At the Seth G.S. Medical College, Bombay:

- ... Training Course in Clinical Pharmacology (November/December, 1989).

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