Multi-photonic imaging analysis of blood flow function in organ microcirculation
- Endothelial disorder and thrombus formation caused by oxidative stress -

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Microcirculation plays an important role to maintain homeostasis and tissue metabolism while it has a lot to concern with every kind of disease. Measurements of blood flow velocity and oxygen tension (pO_2) in the microcirculation levels are essential to elucidate mal-function of the tissue metabolism. In this paper, we proposed a novel multi-photonic imaging system to measure blood flow velocity, vessel diameter, and blood pO_2 simultaneously with high spatio-temporal resolution in parenchymatous organ microcirculation, such as brain, kidney, and liver, by using two or more light sources. Blood flow in the parenchymatous microcirculation was visualized by perfusing fluorescent isothiocyanate (FITC) labeled RBCs and by using a fluorescent microscope. Since absorption and emission spectral peaks of FITC are 450 nm and 520 nm, it was excited by irradiation of a mercury lamp through a band pass filter (450-490 nm). Blood pO_2 was also measured by using luminescent quenching method of phosphorescent molecular probe, Pd-meso-tetra-(4-carboxyphenyl)-porphyrin (Pd-TCPP), which was previously administered to an objective rat via a femoral vein. Pd-TCPP was excited with the second harmonic of a Q-switched Nd-YAG pulse laser (532 nm in wavelength, 6ns in pulse width, 1Hz in pulse recurrent frequency) and the phosphorescence was detected through a long pass filter ($>$ 620nm) using a photo-multiplier. From the phosphorescence lifetime of the emission decay curve, pO_2 was obtained by using Stern-Volmer equation. Oxygen metabolism was also analyzed by means of fluorescent absorption of NADH in the tissues. Additionally, for visualization of flow behavior of platelets and leucocytes, fluorescent dye probes, rhodamine G and CFDASE, were used respectively. Increases in the platelet aggregation and leukocyte adherence were observed in ischemic brain microcirculation. Animal experiments showed effectiveness of the system which provided valuable physiological data concerning in the ischemia-reperfusion process, asphyxia and acute hemorrhage shock, etc. Influence of oxidative stress on the endothelial cells, adherent function of platelet and leukocyte as well as thrombus formation was evaluated in this study.

Session-2

From governmental administration office

2．行政サイドから

座長：南谷晴之（慶応大・理工）

2－1．　血液新法について

丈達泰史（厚生労働省・血液対策課）

2－2．　経済産業省の医療機器関連施策

藤本康二（経済産業省・医療･福祉機器産業室）

Session-3-1

Synthetic antibodies, plasma and proteins

- Cytokines -

3-1

最近臨床応用が認可された人工抗体・抗TNFα抗体

-関節リウマチにおける抗TNFα抗体療法

橋本博史（順天堂大・膠原病内科）

関節リウマチ(RA)は、滑膜関節炎を主徴とする慢性の炎症性疾患で、抗リウマチ薬(DMARD)による治療にも関わらず多関節の破壊や変形、機能障害をみることが多い。

一方、炎症性サイトカイン、特にIL-1とTNFαはRAの滑膜炎と骨関節破壊に関与する重要サイトカインであることが知られている。最近、これらのサイトカインを阻害する生物学的製剤が開発され、RAの治療薬として画期的な効果が示されている。最も効果的な抗サイトカイン療法は、RAの炎症に中心的に働いているTNFαに対する阻害薬である。これには2種類の薬剤が挙げられ、可溶性のリコンビナントTNF-Fc融合蛋白と抗TNFα抗体である。前者にはetanerceptがあげられ、後者には、マウスのFabを用いた抗TNFαキメラ抗体のinfliximabと完全ヒト型の抗TNFα抗体、adalimumabがあげられる。現在、日本ではinfliximabがメトトレキサート(MTX)に反応しないRA患者に使用可能である。しかしながら、使用に際してはMTXとの併用が条件で、使用できる施設は限られている。これらの生物学的製剤の使用により臨床的に早期より急速な改善を認め、その効果は2週目より認められることが多い。さらに、いずれの薬剤も投与1年後の骨破壊はMTXの単独投与に比べ少なく、進行抑制が認められる。しかしながら、infliximabの市販後調査では、敗血症や結核、非定型抗酸菌症、真菌感染、他の日和見感染、脱髄疾患、再生不良性貧血などの有害事象が報告されている。ここでは、抗TNFα療法の特徴と効果、問題点について述べる。

Anti-TNFαagents for the therapy of rheumatoid arthritis

Hiroshi Hashimoto (Juntendo Univ. Dept. of Rheumatology)

Most patients with rheumatoid arthritis (RA) experience a chronic fluctuating course of disease that, despite therapy using disease modifying antirheumatic drug (DMARD), may result in progressive joint destruction, deformity and disability. On the other hand, proinflammatory cytokines, notably interleukin 1 (IL-1) and tumor necrosis factor α(TNFα), play an important role in initiating and perpetuating inflammatory and destructive processes in the rheumatoid joint. Recently, the development of genetically engineered biologic agents that selectively block these cytokines represents a major advance in the treatment of RA.The most clinically effective anti-cytokine agents are antagonists to TNFα, an essential mediator of the cytokine inflammatory cascade in RA. Three anti-TNFα agents have been developed. They are etanercept, which is a recombinant soluble TNF-Fc fusion protein, infliximab, which is a chimeric (mouse-human) anti-TNF monoclonal antibody, and adalimumab, which is a humanized anti-TNF monoclonal antibody. Now it is possible to use infliximab for the patients with RA who do not have a satisfactory response to methotrexate (MTX) in Japan. In this paper, the characteristics, the efficacy and the risks of above biologic therapies are discussed.

Session-3-2

Synthetic antibodies, plasma and proteins

- Synthetic IgG as a therapeutic drug for vasculitis -

3-2-1

急速進行型糸球体腎炎を伴うANCA関連腎炎・血管炎へのIVIg治療効果の検討

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ANCA関連血管炎症候群はしばしば急速進行性糸球体腎炎を呈するが,肺、消化器、脳などの全身血管炎症状も来たし難治性である。本症の治療には強力な免疫抑制療法が必要であるが、高齢者に多く、致命的な治療副作用もしばしば経験される。免疫グロブリン治療(intravenous immunoglobulin treatment; IVIg)は免疫能の調整を行い治療効果を発揮することから従来の治療法を補う有力な導入療法として期待される。１５症例を対象とした治療成績を述べる。【対象】MPO-ANCA陽性患者１５名（男性9、女性６名、72±3歳)。全例に治療前腎生検を施行、組織学的にANCA関連腎炎・血管炎と診断。組織所見をActivity Index, Chronicity Indexを用いて評価した。【方法】導入期治療としてIVIg(乾燥スルホ化ヒト免疫グロブリン) 400mg/kg/day, ５日間施行、後療法として経口ステロイド療法あるいは経口 cyclophosphaminde 投与を行った。IVIg 治療前後の臨床的治療効果判定をBirmingham vasculitis activity score (BVAS)、血清CRP, Creatinine (Cre) を用いて評価した。腎機能の低下率を評価するために、Reciprocal creatinine (1/Cre) の変化率を検討した。【結果】治療前と比較し、IVIg治療後のBVASは有意に低下した (p=0.0001)。またIVIg治療によりCRPは有意に低下した(p=0.0007)。1/Creの変化率は治療後有意に増加し、腎機能の改善が認められた(p<0.05)。IVIgによる重篤な副作用の発現は認められず、その後に行ったステロイドを含む免疫抑制療法後も感染症による予後不良症例は皆無であった。６ヶ月後の時点で透析一例、感染症無し、再発による死亡一例であった。【結論】IVIg治療はMPO-ANCA関連腎炎・血管炎において導入期治療として有効で、患者の予後を改善しうると考えられた。

Clinicopathological analysis of the effect of intravenous immunoglobulin (IVIg) on rapidly progressive glomerulonephritis in the patients with myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-related and vasculitis

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Myeloperoxidase (MPO) -antineutrphil cytoplasmic antibody (ANCA) -related glomerulonephritis (GN) and vasculitis frequently involvee multiple organs such as lung, gastrointestinal tract and brain. In order to treat this deteriorative diseasee, it necessitates aggressive immunosuppressive treatment including steroid and cyclophosphamide; however, such treatment is not always available to elderly or immunocompromised patients. Intravenous immunoglobulin (IVIg) before the use of immunosuppressive agent is an alternative therapy which can modulate the immune system without severe side effects. PATIENTS: Fifteen patients with serologically and histologically confirmed ANCA-related GN / vasculitis (Nine men and Six women; age 72±3 y.o.) have been treated with IVIg (Freeze-dried sulfonated human normal immunogloblin, Kenketsu Venilon I, Teijin Ltd., Japan; 400mg/kg/day for 5 consecutive days) before the beginnning of immunosuppressive therapy. Effects of IVIg were evaluated by Birmingham vasculitis score (BVAS) , serum C reactive protein (CRP) and creatinine (Cre) levels, change of reciprocal creatinine (1/Cre) rate before and after IVIg treatment. All of there evaluations were performed. before starting the immunosuppressive therapy, RESULTS: IVIg treatment significantly reduced BVAS ($p=0.0001$) and CRP values ($p=0.0007$). The change of 1/Cre rate significantly increased after IVIg treatment ($p<0.05$). Following immunosuppressive therapy (moderate dose of steroid and partial cyclophosphamide) have succeeded to provide the remission of the disease without any severe infectiou complications. At 6 months after IVIg, one patient have undergone hemodialysis One patient has died due to the relapse of vasculitis.. CONCLUSION: IVIg is the potent induction therapy for patients with ANCA-related GN and vasculitis followed by favorable prognosis without any detrimental side effect.

3-2-2

川崎病とガンマグロブリン療法

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川崎病は67年川崎富作博士により最初に報告された小児の熱性発疹性疾患である。基本的には系統的血管で、中型動脈、特に心臓を養う冠動脈に強い炎症が起こり、冠動脈瘤が形成されるのが特徴である。冠動脈瘤は冠動脈瘤内血栓などによる急性心筋梗塞の危険性をはらむものである。世界中の研究者の努力にもかかわらず原因は未だに不明である。患者は世界中に見られるが日本に断然多く、これに韓国、台湾、米国が次いでいる。最新の川崎病全国調査によると、日本での年間発生数は約８千名で、３２年間の累計で２０万人弱である。治療法は、60年代にはステロイドが用いられた。その後80年代にはアスピリン治療が主流になった。それでも冠動脈瘤が約40％の例に見られたので、新たな治療法が模索された。そして８４年に免疫グロブリン療法（ＩＶＩＧ）の有用性が京都大学の古庄らにより報告された。８９年に健康保健で認められた投与量は当初200ｍｇ/ｋｇ５日間の分割投与であった。９４年米国でニューバーガーらにより2g/ｋｇ単回投与のより高い有用性が報告されて、現在の世界標準になった。日本ではこの報告より約１０年遅れで、昨年よりこの大量単回投与が健康保健の適応になった。免疫グロブリン療法の効果には投与量依存性が見られる。現在はこの最新治療法で冠動脈瘤の出現頻度が約1/3に減少した。しかし免疫グロブリンの作用機序は良く判明していない。

今回作用機序も含めて、川崎病と免疫グロブリン療法の現状を報告する。

Immunoglobulin tretment for Kawasaki disease

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Kawasaki disease (KD) is an acute febrile disease of childhood first described by Dr. T. Kawasaki in 1967. KD causes severe systemic vssculitis but predominantly affecting the medium-sized arteries, especially coronary arteries. KD patients develop coronary artery abnormalities (CAA) including aneurysms with the potential for the development of coronary thrombosis and acute myocardial infarction. The cause of KD is still unknown despite efforts of many investigator of the world. Although the occurrence of the patients was reported from all over the world, the incidence of KD is highest in Japan and the following countries are Korea, Taiwan and USA. According to the latest nation wide survey of KD in Japan, recent annual incidence of KD is 8,000 in number and approximately 20,000 cases have been reported since 1960s.

Regarding the treatment, corticosteroids was used in 1960s. Aspirin treatment became the mainstay in 1980s. The incidence of CAA in Aspirin treatment was about 40%. The successful immunoglobulin (IVIG) treatment using 200mg/kg for 5days was reported by Prof. Furusho in Japan in 1984. Dr. Newburger reported more successful result using IVIG of 2g/kg for one day in 1994 and this single high dose treatment became the standard treatment for KD. About 10 years later since the Newburger's report, Japanese government approved this treatment in Japan in 2003.

The efficacy of IVIG is dose dependent. The incidence of CAA decreased from 40% to 15% nowadays using this single high dose IVIG. The mechanism of IVIG for KD is still not clearly understood. I would like to present the recent aspects of IVIG treatment including some mechanism of IVIG.

3-2-3

IVIGが奏功した小児重症紫斑病性腎炎の1例

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紫斑病性腎炎は小児の2次性腎炎の代表的な疾患で小児腎不全の約7％を占める。重症紫斑病性腎炎は予後不良であり積極的な治療を要するが治療法は確立していない。
今回我々は重症紫斑病性腎炎の治療経過中に敗血症による急性腎不全を合併した症例に対し大量ガンマグロブリン療法（IVIG）を行い良好な経過が得られたので報告する。
症例は13歳女児。紫斑、腹痛、関節痛および著明な蛋白尿（19g/日）、腎機能障害を認め紫斑病性腎炎と診断した。腎生検では著明な半月体形成（64%）を伴うメサンギウム増殖性腎炎であり、ISKDC IVbと診断しメチルプレドニゾロンパルス療法を3クール行った。蛋白尿が持続するためパルス-ウロキナーゼ療法を2クール追加したが、敗血症による急性腎不全を合併し血液浄化療法を必要とした。IVIG（1g/kg/日）を行ったところ、腎機能は改善し蛋白尿も激減した。組織学的にも半月体は減少し、IgA沈着もほぼ消失した。
治療抵抗性の重症紫斑病性腎炎に対してIVIGは有効な治療法の一つと思われた。

Successful treatment of severe Henoch-Schonlein purpura nephritis with high-dose immunoglobulin therapy

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Purpura nephritis is the common form of secondary glomerulonephritis and result in 7% of renal failure in children. As a severe purpura nephritis has poor prognosis in children, an effective therapy has been expected but has not been established yet. We reported a case with Purpura Nephritis who successfully treated with high-dose immunoglobulin therapy.

A 13-year-old girl was admitted for the evaluation of purpura, joint pain, abdominal pain and massive proteinuria. Laboratory investigations showed mild renal insufficiency and nephrotic proteinuria (19g/day). Renal biopsy showed severe proliferative glomerulonephritis with crescent formations (64%) and mesangial immunoglobulin A (IgA) deposition. She was diagnosed as ISKDC grade Ⅳb of Henoch-Schonlein purpura nephritis and was treated by steroid and steroid-urokinase pulse therapy which resulted in a partial improvement of proteinuria (2-3 g/day). After the steroid therapy, she complicated with sepsis and acute renal failure. Hemodyalysis and high-dose intravenous immunoglobulin therapy (1g/kg/day) apparentely improved her renal function and proteinuria. Renal rebiopsy confirmed an improvement of crescent formations and mesangial IgA deposition. High-dose immunoglobulin administration would be one of the considerable therapies for the patient with Henoch-Schonlein purpura nephritis, who is intractable to conventional treatments.

3-2-4

MPO-ANCA 関連血管炎の発症機構とガンマグロブリン開発

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血管炎の発症は、myeloperoxidase(MPO)を抗原とするMPO-ANCAの血中レベルの上昇や、活性化好中球の関与がその発症に重要である。しかし、血管炎発症における好中球自己抗体や活性化好中球の役割は未だ解明されていない。急性進行性半月体形成性腎炎や川崎病の末梢好中球は、活性酸素産生能やMPOの放出能活性が上昇しており、末梢好中球は、活性化状態にあり、血管炎の発症に活性化好中球が深く関与していることを示唆している。一方、臨床マーカとして利用されているMPO-ANCAの抗体価の変動は、病初期の後は、疾患の病態と必ずしも連動しないことから、MPO-ANCAのクローンが病態に関与している可能性があるところから、エピトープによりクロナリティを調べた。その結果、MPOのH鎖のNおよびC末端に単独で反応するクローンが病態と関連があることが判明した。このクロナリティーに変化を及ぼすことが考えられる大量グロブリン治療免疫グロブリン治療(IVIg)の有効性が検討され、IVIgが有力な導入療法として期待されている。

Development of MPO-ANCA related vasculitis and its treatment with IVIG

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Activated neutrophils may cause the development of vasculitis. Patients with MPO-ANCA related glomerulonepheritis (GN) and Kawasaki disease showed an increase of superoxide production and myeloperoxidase (MPO) release from neutrophils in peripheral blood, showing circulation of activated neutrophils. In addition, the antibodies against MPO and proteinase-3 (PR3) in neutrophil granules, anti-neutrophil cytoplasmic antibodies (ANCA), have been demonstrated to be associated with the development of vasculitis. Moreover, a higher percentage of MPO-ANCA in Japan than that in Europe has been reported. We have demonstrated that MPO is an antigen of MPO-ANCA using MPO-KO mice. However, it is not exactly related with disease activity in the late phase. Therefore, we have estimated the clonality of MPO-ANCA related with disease activity using epitope analysis, showing epitopes of MPO-ANCA reacting with N, and or C-terminals are related with the activity. The treatment with IVIg for vasculitis has been demonstrated in Japan, because of change in clonality of MPO-ANCA, probably.

3-2-5

人工グロブリンの分子設計と合成

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我々は、従来技術では困難であったバクテリア細胞質での抗体分子の合成技術を開発した。FKBP(FK506 binding protein)は免疫抑制剤 FK506 のターゲット分子と知られていると共に、蛋白質折り畳みの後期過程の律速段階であるプロリン残基の立体異性化を触媒する Peptidyl prolyl *cis-trans* isomerase (PPIase)活性を有する。古細菌由来の FKBP は蛋白質折り畳みの初期段階にポリペプチドの疎水性領域と相互作用することで、凝集体の形成を抑制するシャペロン活性も持ち合わせており、この機能が PPIase 活性と独立したものであることを明かにした(1, 2)。この古細菌型 FKBP の機能を蛋白質発現に利用するために FKBP のC末端に目的蛋白質を融合させる発現系を開発した(3)。本発現系によって scFv (single chain Fv)や Fd (VH-CH1) 等の抗体ﾌﾗｸﾞﾒﾝﾄの大腸菌細胞質可溶性画分での大量合成が可能となった。

血漿由来の免疫グロブリン大量静注療法 (IVIg)は ANCA (anti-neutrophil cytoplasmic antibody)が関与する川崎病、血管炎、腎炎の治療に有効であることが知られている(4)。しかしながら、その安全性、副作用や安定的供給面での問題を抱えており、人工グロブリンの開発は急務である。本シンポジウムではグロブンリン製剤の人工化ストラテジーについても述べたい。

Design and Synthesis of Recombinant Immunoglobulin

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We developed a new method to express recombinant antibodies in bacterial cytoplasm, which had been difficult in conventional technologies. The FKBPs are the targets of an immunosuppresant FK506, and catalyze the *cis-trans* isomerization of peptidyl prolyl bonds in polypeptides, which is a rate-limiting step in protein folding. We have showed that archaeal FKBPs protect the aggregation of polypeptides in the early stage of protein folding, and this chaperone function is independent of their PPIase (peptidyl prolyl *cis-trans* isomerase) activity (1, 2). We developed the recombinant protein expression system in which target proteins are expressed as a fusion form connected with the C-terminus of an archaeal FKBP (3). This system enables to express antibody fragments, scFv (single chain Fv) , Fd (VH-CH1), and some eukaryotic aggregation-prone proteins in the soluble fraction of bacterial cytoplasm.

While IVIg (intravenous immunoglobulin) treatment is effective for ANCA (anti-neutrophil cytoplasm antibody)-associated Kawasaki disease, vasculitis, and glomerulonephritis (4), immunoglobulin from plasma has the problems in safety, side effects and stable supply. Artificialization of immunoglobulin is pressing need. The strategy of recombinant polyclonal Fv immunoglobulin would be also reported in this presentation.

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Session-4

Special Lecture

Pathogen Safety: From Blood Donation to IVIG Ready for Infusion and Mechanism of Action of IVIG

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Pathogen safety: Intravenous immunoglobulin preparations (IVIGs) of today have a high safety profile. The current mainstays of pathogen safety of plasma products are: (A) donor selection in order to prevent donations by individuals at risk; (B) screening of donations in order to exclude potentially infectious donations; (C) in-process control in order to withhold a positive pool from fractionation; (D) validated steps for elimination and/or inactivation of potentially present infectious agents; (E) equipment cleaning and batch to batch segregation; (F) traceability of lots and (G) strict compliance with Good Manufacturing Practice and Quality Assurance.

Donor selection: The main safety measures in donor selection are donor education, continuous adaptation of donor questionnaires, physical examination of the donor and the confidential self-exclusion of donated blood/plasma from further processing.

Mass screening of donations: The mandatory testing for anti-treponema and liver enzymes in blood/plasma is complemented by antibody testing for virus markers such as HIV 1&2, HAV and HCV and screening for hepatitis B surface antigen (HBsAg). More recently nucleic acid testing (NAT) was introduced in order to minimize the so called window period. Presently "five-NAT" is applied to plasma fractionated for the Japanese market: HIV-RNA and HCV-RNA, HBV-DNA, HAV-RNA and parvovirus B19 DNA.

Validation of virus elimination/inactivation: In validation studies, the safety of a product has to be demonstrated on a laboratory scale by spiking starting materials and showing the elimination of the virus over the various steps of the process. It is assumed by authorities that the application of different principles of virus removal and inactivation during fractionation and polishing makes a product pathogen safe. There are only three basic principles of virus elimination: (A) partitioning; (B) inactivation and (C) elimination based on size. There exist various methods within the frame of these principles that can be used to achieve virus safety of IVIG. All manufacturers use partitioning to eliminate viruses, applying the methods of protein precipitation, filtration in presence of filter aids and column chromatography. The methods of virus inactivation used are: (A) solvent/detergent treatment resulting disruption of the viral envelope, a process which might however fail with viruses having several layers of envelope (poxviridae); (B) caprylate induced incorporation of non-ionized molecule into the viral envelope and eventual disruption of the envelope; (C) disruption of the envelope by heat, i.e. pasteurization and (D) ionic disruption of the envelope and conformational changes of viral proteins needed for docking of virus to the target cell e.g. by low pH treatment. The primary target of all these inactivation methods is the viral protein involved in the infection of the host cell. Disintegration of the virus envelope destroys such structures efficiently and only methods C and D have a potential for inactivation of non-enveloped viruses. One of the key points of such virus inactivation studies is to show kinetics of inactivation. All manufacturers of IVIG use one or more of the above virus inactivation methods. Nanofiltration was recently introduced into large scale manufacturing of IVIG, to add further on safety gained by partitioning and inactivation. The principle relies on virus size and is also able to remove small

non-enveloped viruses under certain conditions.

Safety of IVIG in regards of transmissible spongiform encephalitis (TSE) agent: Today the inactivation of the TSE agent is not possible without destruction of the biological activity of the product. Thus, only the principles of partitioning and size exclusion can be applied to eliminate TSE agents during manufacturing of IVIG. Studies by various groups have shown the various cold-ethanol fractionation methods (Cohn and Kistler-Nitschmann) produce similar reductions of a model TSE agent. The overall reduction during fractionation and filtration processes can be as high as >9 log. Nanofiltration might further reduce the risk of transmission of the TSE agent by IVIG as was demonstrated by model experiments utilizing brain-derived infectivity.

Mechanism of action: IVIGs help in host defence against invading pathogens and are at the same time immunomodulating and antiinflammatory.

Host defence: The titre and the affinity of transfused antibodies are relevant in host defence. Considerable lot to lot fluctuation in titres of specific immunoglobulins is inherent to all IVIGs, except the titre of a selected specificity is adjusted to a given level. Adjustment in titre of one specificity does not prevent lot to lot fluctuation of all other specificities. Furthermore, with plasma pool donor size increasing from 8,000 to 60,000 such lot to lot fluctuation in titres does not diminish. There is little known about lot to lot variation in affinity of specific antibodies.

Immunomodulatory and antiinflammatory potential: It was in 1981 when it became evident that an autoantibody mediated disease (ITP) can be ameliorated by polyclonal immunoglobulins prepared from a plasma pool of healthy donors. The following was dedicated from this observation: (A) transfused polyclonal IgG is able to inhibit the effects of a pathogenic autoantibody, and (B) for the sake of benefit of the recipient, transfused IgG must be able to recognise the recipient's "immunological structures" in an allo-reactive manner. The IgG molecules in IVIG able to interact with the recipient's immune system mainly belong to the natural antibodies and are either part of the network of the proteins with variable regions (T cell receptor, B cell receptor, immunoglobulins) or interact with cell surface molecules and plasma proteins of the native immune system. The knowledge about interactions of IVIG with the recipient's immune system is ever growing. These multiple reactions represent IVIG's therapeutic potential, i.e. to interact at multiple sites with a derailed immune network and being even able to cover redundancies of the system. Indeed, at occasion of any infusion it is inevitable that all of the interactions occur, although to various extents. The extent in intensities of individual interactions depends on the actual condition of the recipient's immune system. The individual interaction might be week and might have a minor effect. However, the multiplicity of the interactions apparently is that what sums up to a therapeutic potential of IVIG.