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History of Ig Therapy

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Passive Immunization

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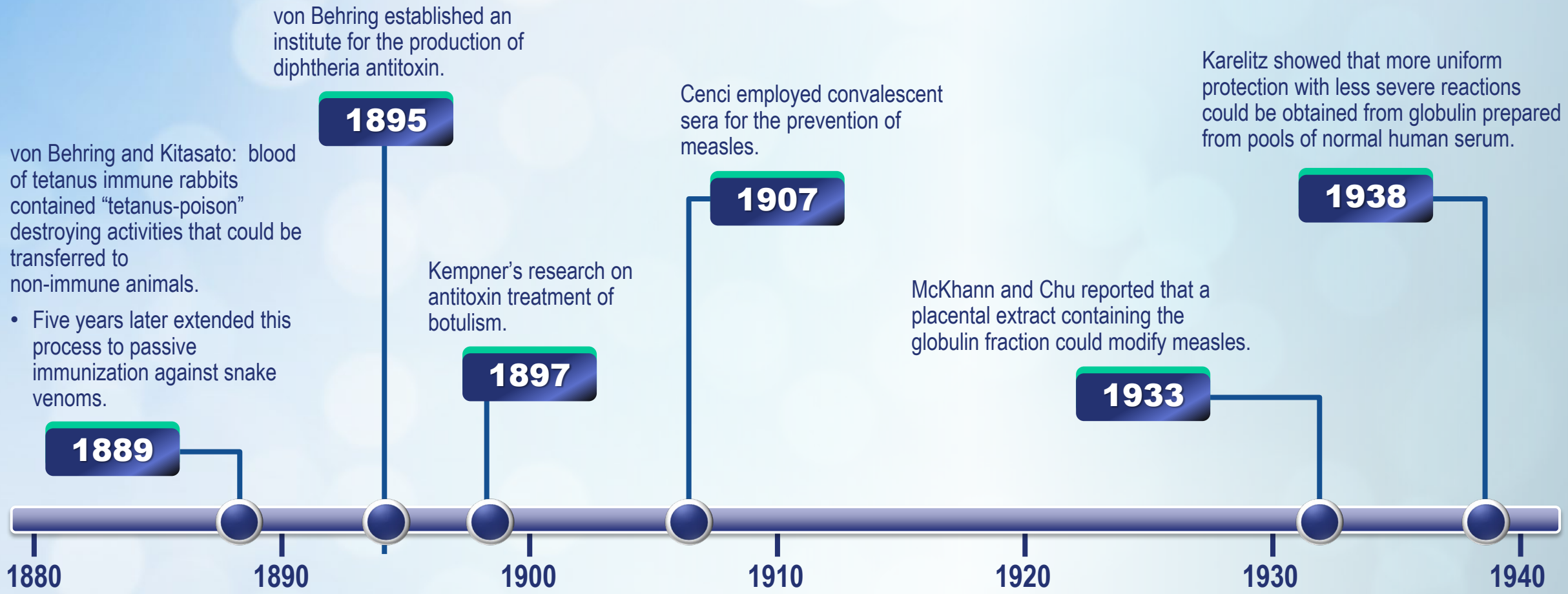

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Evolution of Gammaglobulin Route of Administration

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First IVIG Preparations

- **Research in the late 1970's led to an acceptable IVIG preparation**
  - Trace amounts of proteases to dissociate aggregates
  - Chromatographic purification of the IgG
  - Stabilize the IgG by: trace pepsin, addition of sugars or amino acids (glycine), or albumin
- **Commercial preparations approved by the FDA in 1981**
  - Gamimmune – **pH 4 plus glycine and maltose (Cutter)**
  - Sandoglobulin – **transient low pH, trace pepsin, stabilized with sucrose (Sandoz)**

Composition of Currently Available IVIG Products

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- **Donor pool**
  - Derived from 1,000-10,000 donors
    - May be as many as 60,000 donors (limit placed by FDA in 2000)
  - Source versus recovered plasma
- **Composition**
  - Monomeric IgG (>95%) with small amounts of dimeric and polymeric IgG
  - Small amounts of IgM and IgA present; varies with product
- **Antibody content**
  - One gram of IVIG contains $4x10^{18}$ molecules of antibody
  - $>10^7$ specificities to a broad range of bacterial and viral pathogens

Amino Acid Stabilized	Other Stabilizers
Asceniv – glycine	Flebogamma – sorbitol
Gamunex-C – glycine	Octagam – maltose
Gammagard Liquid – glycine	Gammaplex – D-sorbitol
Privigen – proline	Gammagard SD – glucose + sodium

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Common Adverse Reactions to IVIG

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- Early IVIG products had 10-15% severe adverse reactions
- Reactions often related to the speed of the infusion and/or minor contaminants in the IVIG
  - Fever; chills; facial flush
  - Tachycardia; palpitations; chest tightness or chest pain
  - Anxiety; nausea; abdominal pain
  - Dyspnea; back pain; arthralgia; myalgia
  - Hypotension; shock
- May occur 6–24 hours after the completion of the infusion
- Side effects of more recent products are milder (10–15%) and occur less frequently (<1%)
- Occur most commonly in newly diagnosed hypogammaglobulinemia patients, or in patients with chronic infection, e.g. bronchitis

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Eibl M and Wedgwood RJ Intravenous Immunoglobulin: A Review. 1989

"Mild" Adverse Events

- Mechanisms
  - Activation of complement by IgG aggregates
  - Antigen-antibody complexes
    - Heavy antigenic (bacteria) loads, e.g. CVID
  - Vasoactive proteins in IVIG as "contaminants"
    - Prekallikrein activator and kallikrein
    - Factor XIa
- Risk factors[1]
  - IgG peak
    - Dose
    - Infusion rate

1. Wasserman RL. JACI:IP 4(6):1076-1081. 2016

IVIG Product Class Warnings and Serious Adverse Reactions[1-3]

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Anaphylactic Reaction – Contraindication	• IgA-deficient patients with IgE antibodies to IgA and a history of hypersensitivity
Thromboembolic Events – Boxed warning	• May be due to increased viscosity/osmolality • One or more underlying risk factors identified • Factor XIa pro-coagulant activity
Renal Failure – Boxed Warning	• Probably due to osmotic injury in susceptible patients with one or more underlying risk factors • Highly associated with sucrose containing products
Aseptic meningitis – Warning	• Migraine is risk factor • Observed with high dose, fast rate
Hemolysis – Warning	• Positive Coombs test (products contain isohemagglutinins) • One or more underlying risk factors

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1. Nydegger UE et al. *Drug Saf.* 1999;31(3):171-185. **2.** Pierce LR, et al. *Transfus Med Rev.* 2003;17:241-251. **3.** Ballow M. *Am J Health Pharm.* 2005;62(16 Suppl 3):s12-8

Minimizing the Risks of IgG Side Effects

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- **Severe, life-threatening side effects**
  - Age – avoid other risk factors in older patients
  - Diabetes or kidney disease – no CHO containing products
  - Thrombosis history – limit dose per infusion, limit infusion rate
  - Cardiac disease – avoid sodium containing products
- **General risk factors**
  - Decrease the dose per infusion
  - Decrease infusion rate
- **SCIG** – risks appear to be lower than IVIG, but not zero
- **fSCIG** – risks appear to be lower than IVIG, but not zero

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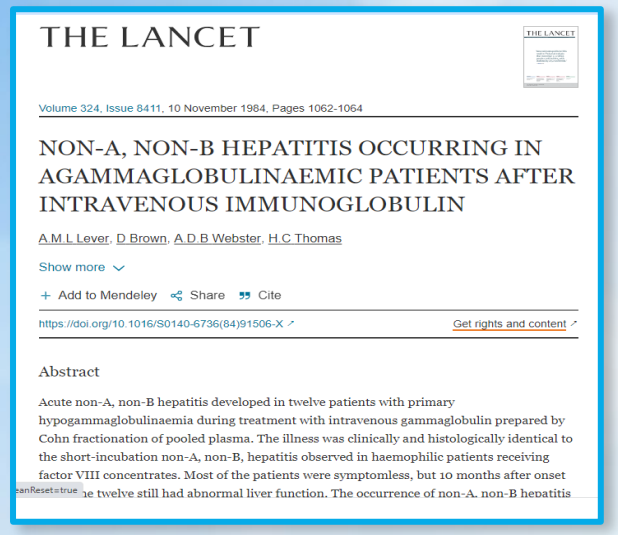
History of IVIG Viral Safety



THE LANCET

Volume 324, Issue 8411, 10 November 1984, Pages 1062-1064

NON-A, NON-B HEPATITIS OCCURRING IN AGAMMAGLOBULINAEMIC PATIENTS AFTER INTRAVENOUS IMMUNOGLOBULIN

A.M.L Lever, D Brown, A.D.B Webster, H.C Thomas

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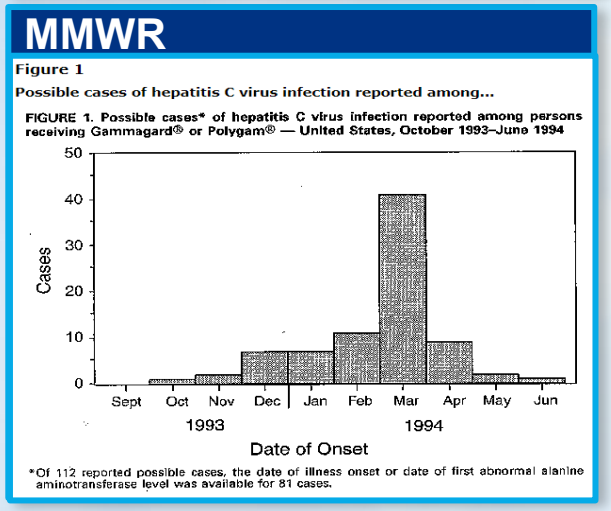
https://doi.org/10.1016/S0140-6736(84)91506-X Get rights and content

Abstract

Acute non-A, non-B hepatitis developed in twelve patients with primary hypogammaglobulinaemia during treatment with intravenous gammaglobulin prepared by Cohn fractionation of pooled plasma. The illness was clinically and histologically identical to the short-incubation non-A, non-B, hepatitis observed in haemophilic patients receiving factor VIII concentrates. Most of the patients were symptomless, but 10 months after onset the twelve still had abnormal liver function. The occurrence of non-A, non-B hepatitis



MMWR

Figure 1

Possible cases of hepatitis C virus infection reported among...

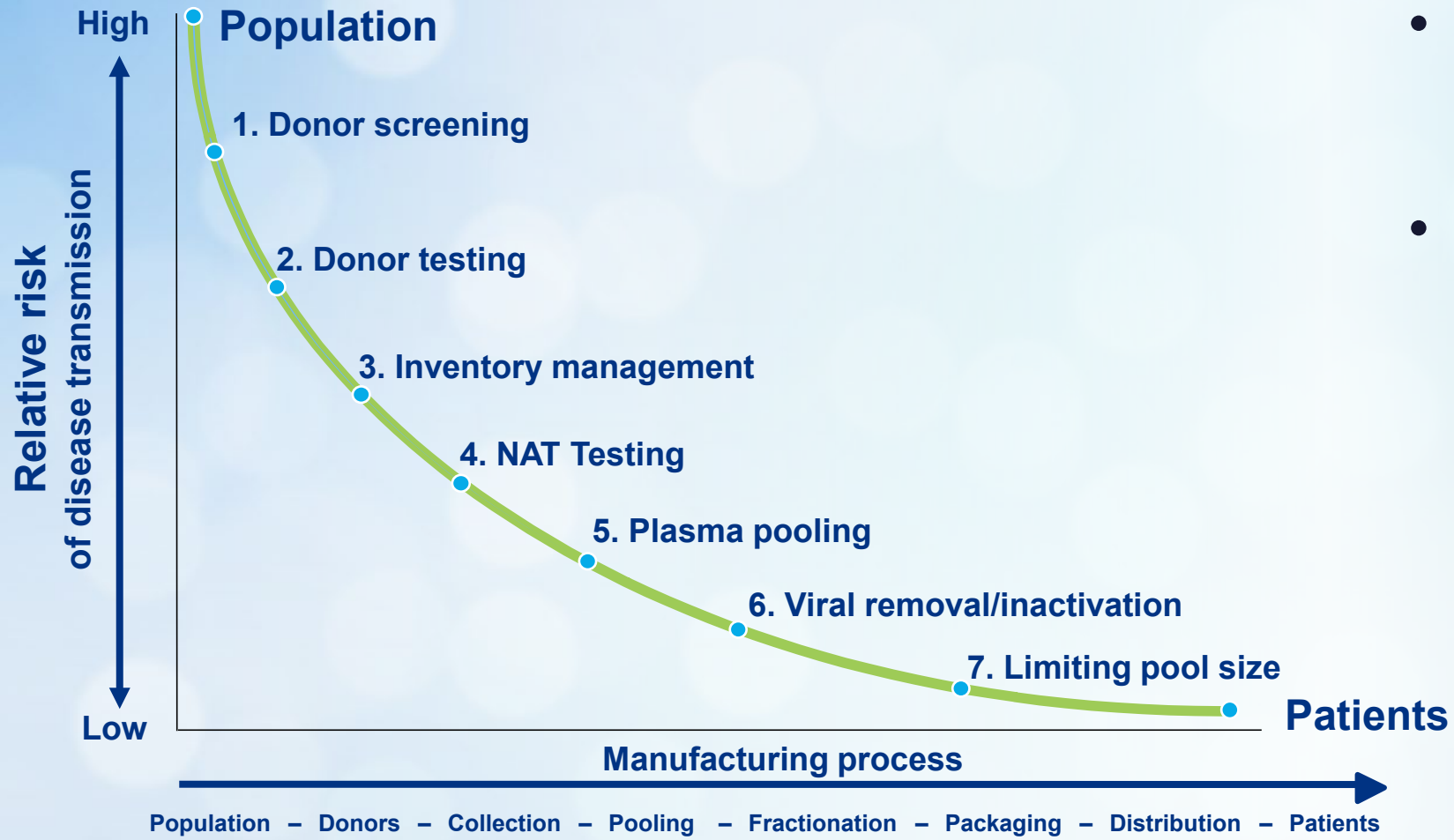
FIGURE 1. Possible cases* of hepatitis C virus infection reported among persons receiving Gammagard® or Polygam® — United States, October 1993–June 1994

*Of 112 reported possible cases, the date of illness onset or date of first abnormal alanine aminotransferase level was available for 81 cases.

- Four clusters of non-A, non-B hepatitis patients who reported receiving IVIG products
- Specific manufacturing procedures implicated in contaminated lots
- Changed manufacturing process to include a solvent-detergent treatment designed to inactivate lipid enveloped contaminating viruses
- No reported cases of transmission of HIV by a licensed product – partitioned out by the ethanol precipitation procedure

1. The Lancet 1984; 8411:1062-1064. **2.** MMWR July 22, 1994 / 43(28);505-509

Approaches to IVIG Pathogen Safety



- Pre-production
  - donor and plasma screening and testing
- Production
  - Virus inactivation – SD, caprylate, pH4 + pepsin, pH 4.25 x 21 days @ 25C, 10h@60C
  - Virus removal – cold ETOH partition, nanofiltration

Biologicals. 2007 Mar; 35(1): 35–42. doi: 10.1016/j.biologicals.2006.01.002
PMCID: PMC7129354 PMID: 16581263

Concerns About Transmissible Spongioform Encephalopathies (TSE) – Prion Disease

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- Creutzfeldt-Jakob Disease (sporadic):
  - No evidence transmitted by blood products
- New variant CJD
  - Emerging pathogen in UK and Europe, 1996 – 2000
    - Mad cow disease
- Quarantine of IVIG product caused shortage in 2000
- Changed GMP to add depth filtration and nanofiltration in purification steps of Ig products

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Thromboembolic Events (TEE)

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NAPTT, non-activated partial thromboplastin time.

1. Daniel GW, Menis M, Sridhar G, et al. *Transfusion*. 2012 Oct;52(10):2113-21. **2.** Funk MB, Gross N, Gross S, et al. *Vox Sang*. 2013 Jul;105(1):54-64. **3.** Oviedo AE, Bernardi ME, Guglielmone HA, et al. *Transfus Med Hemother*. 2015 Nov;42(6):397-402.

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Risk Factors for Thromboembolism

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Infusion factors

- Large dose, e.g. treat autoimmune disorders (neurology)
- Rapid infusion
- No pre-infusion or post-infusion hydration
- First infusion

Patient factors

- Hypercoagulable state
- Indwelling catheters
- Cerebrovascular or cardiovascular disease
- Diabetes
- High lipids/cholesterol
- Hypertension
- Prior history of thrombosis
- Estrogen use
- Smoking

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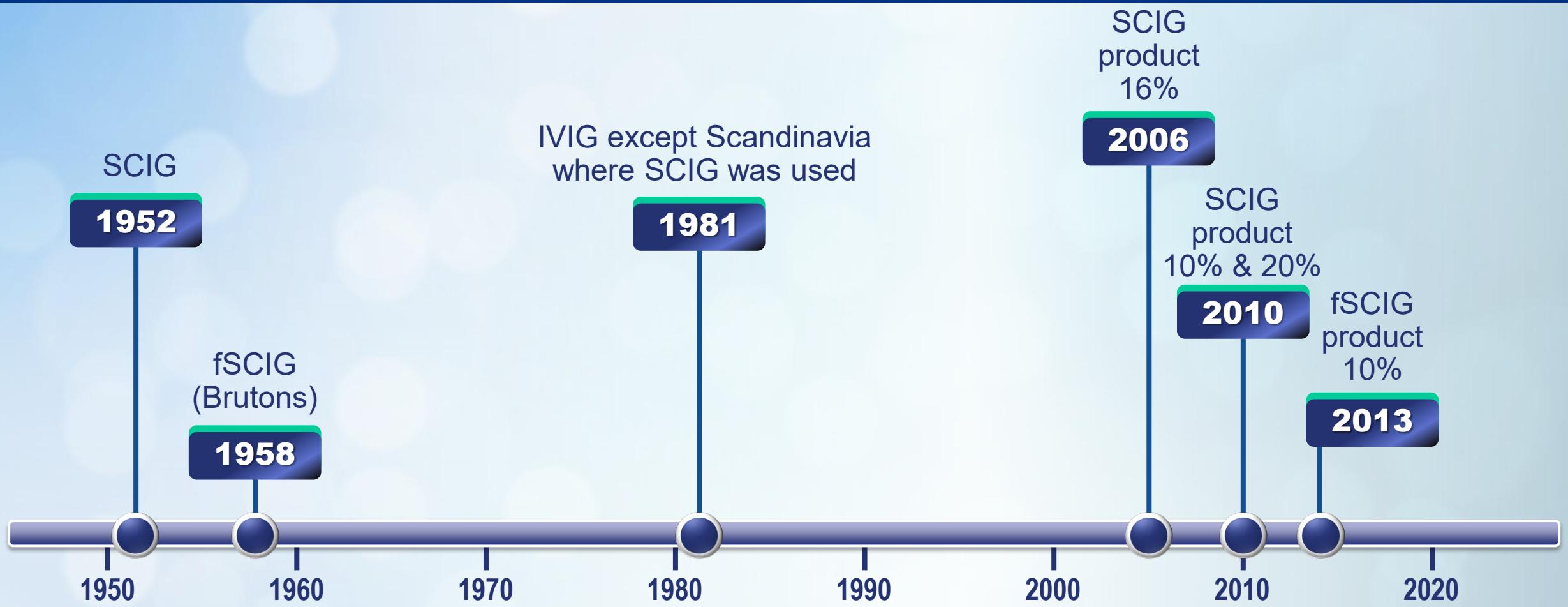
Evolution of IgG administration



US FDA-Approved Indications for IVIG

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IVIG is recommended for a limited number of FDA-approved indications

- **Chronic inflammatory polyneuropathy (CIDP)**
- **Multifocal motor neuropathy**
- **Dermatomyositis**
- Primary immunodeficiency disease
- Idiopathic thrombocytopenic purpura
- Kawasaki disease
- B-cell chronic lymphocytic leukemia for recurrent bacterial infections
- Pediatric HIV for recurrent bacterial infections
- Bone marrow transplantation
  - Acute graft-versus-host disease
  - Interstitial CMV pneumonia
  - Infections

Note that not all products are approved for all indications

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When Do Product Characteristics Make a Difference?

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- Pre-existing **kidney disease, diabetes or hypertension**
  - Avoid carbohydrate containing products.
- **Heart disease**
  - Prefer low/no sodium
  - Isosmolal
  - Higher concentration/lower infusion volume
- At risk for **hyperviscosity** – MGUS, myeloma
  - Prefer low/no sodium
  - Isosmolal
  - Lower concentration
- **IgE anti-IgA antibodies**
  - Undetectable/low IgA content

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Summary

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	Intravenous Immunoglobulin (IVIG)	Subcutaneous Immunoglobulin (SCIG)	Hyaluronidase Facilitated Immunoglobulin (fSCIG)
Indications	Adult and pediatric PI, **ITP, KD, CLL, DM, CIDP, MMN**	Adult and pediatric PI, **CIDP**	Adult and pediatric PI patients
Administration	Healthcare professional administered	**Self-administered**	**Either** self-administered or a healthcare professional administered
Frequency	Usually given **every 3-4 weeks**	**Daily to every 2 weeks**	Usually given **every 3-4 weeks**
Infusion time	Typically **2-6 hours to infuse**	Can take **5 minutes to 2 hours to infuse or inject**	Usually **1-2 hours to infuse**
Location of care	Can be infused at **home**, in a hospital or an **outpatient infusion center** depending on insurance and patient preference	Usually administered in a **home** setting after the patient is trained to be independent	Can be infused at **home or in an outpatient infusion center** depending on insurance and patient preference
Side effects	**5-15% of patients experience systemic AEs**; most commonly headache, myalgia, malaise. Side effects may be delayed. AEs can be mitigated by pre-hydration, reduced infusion rate and pre-medications	**Systemic AEs in 1-3% of patients**. Local AEs; erythema, pruritis, pain, induration occur at least once in most patients but lessen or resolve over time.	**Systemic AEs in 7% of patients**. Local AEs; erythema, pruritis, pain, induration occur at least once in most patients but lessen or resolve over time. Because of the large infusion volume, edema resolves over 24-72 hours.

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IVIG as an Immunomodulator: High Dose IVIG in Children with ITP

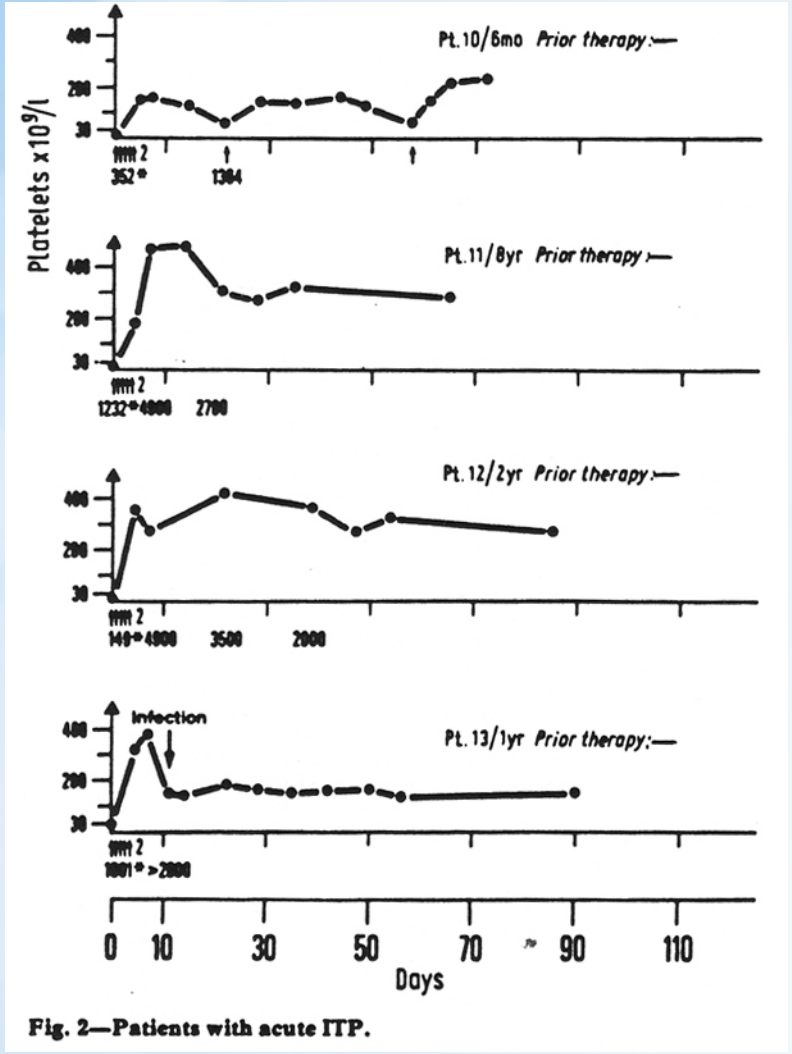

Fig. 2—Patients with acute ITP.

THE LANCET, JUNE 6, 1981

HIGH-DOSE INTRAVENOUS GAMMAGLOBULIN FOR IDIOPATHIC THROMBOCYTOPENIC PURPURA IN CHILDHOOD

P. IMBACH
V. d'APUZZO
A. HIRT
E. ROSSI
M. VEST
S. BARANDUN
C. BAUMGARTNER
A. MORELL
M. SCHÖNI
H. P. WAGNER

70% of IG Used “Off-label”

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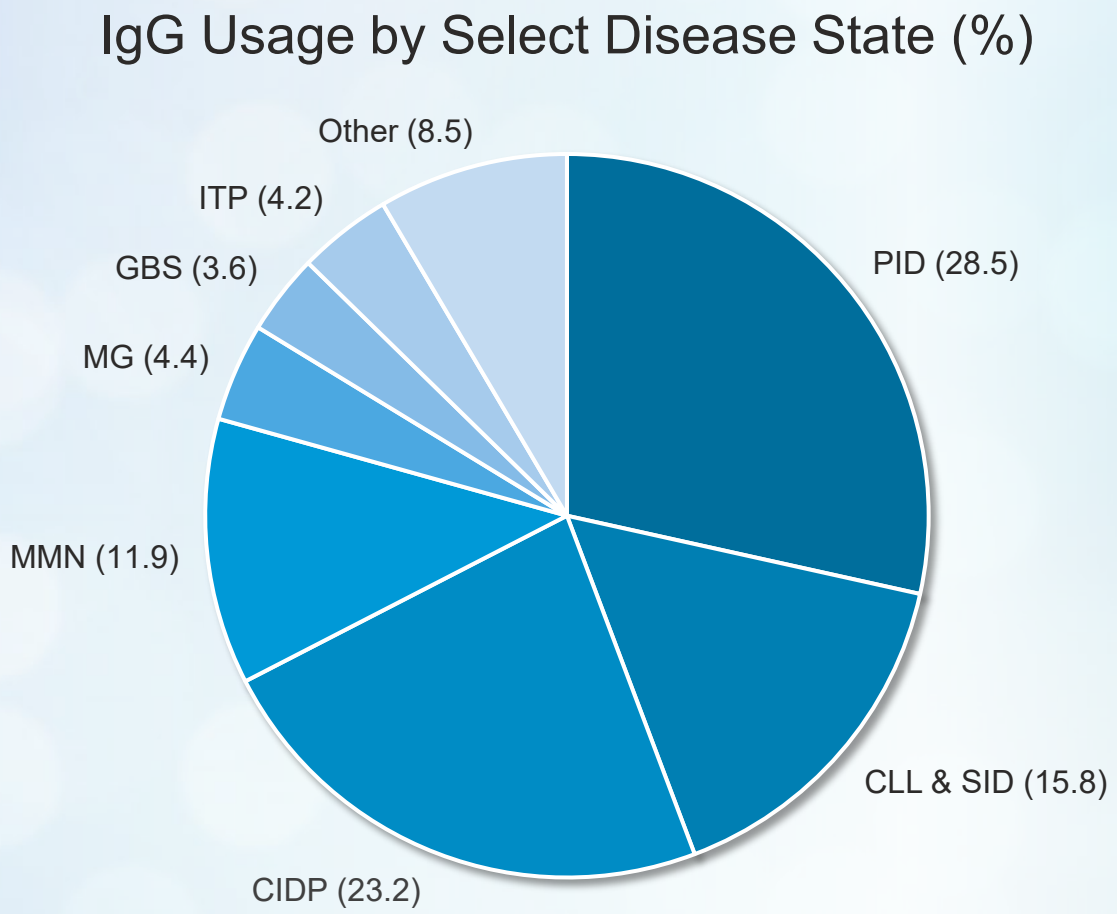

Rossi’s Principles of Transfusion Medicine, Sixth Edition. Edited by Toby L. Simon, Eric A. Gehrie, Jeffrey McCullough, John D. Roback, and Edward L. Snyder.© 2022 John Wiley & Sons Ltd. Published 2022 by John Wiley & Sons Ltd.

Companion website: www.wiley.com/go/simon/Rossi6. Melvin Berger, Departments of Pediatrics and Pathology, Case Western Reserve University, Cleveland, OH, USA. CHAPTER 23, Immunoglobulin products.

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Recognized* Neurological Uses of IVIG

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Guillain Barre Syndrome

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Multifocal Motor Neuropathy

Dermatomyositis

Myasthenia Gravis

*Recognized does not infer FDA approval

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IVIG Works in Multiple Ways to Disrupt the Inflammatory Process of Autoimmune Presentations

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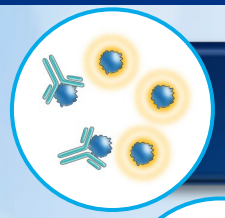
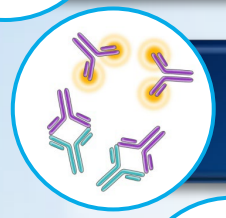
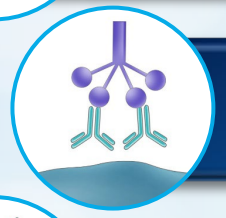


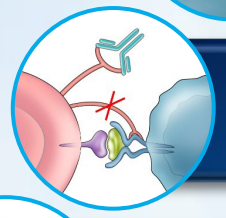
Downregulation of inflammatory cytokines[1]



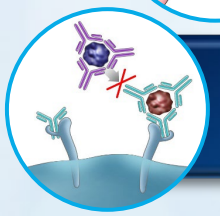
Neutralization of pathologic autoantibodies[3]



Inhibition of complement activation[1]



Regulation of T-cell and B-cell activation[3]



Blockade/modulation of Fc receptors[3]

[a]The precise mechanism of action of IVIG in treatment of CIDP has not been fully elucidated.

1. Dalakas MC. *Nat Rev Neurol*. 2011;7(9):507-517. **2.** Durandy A. *Clin Exp Immunol*. 2009;158(suppl 1):2-13. **3.** Ritter C. *J Neuroinflammation*. 2015;12:148.

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Guillain Barre Syndrome

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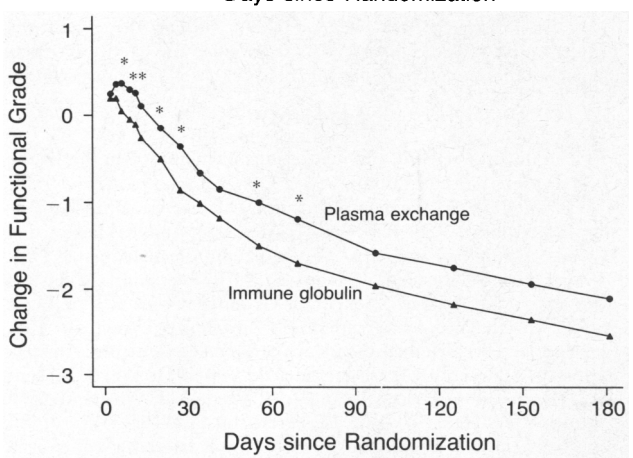
immune-mediated diseases.[11-14] The biologic effects of high-dose immune globulin in these conditions have not been fully elucidated, but it is clear that the drug may influence the immune system in many ways.[13-19] It is not possible to predict the mechanism that might be beneficial in Guillain–Barré syndrome, since the

From the Department of Neurology, Academic Hospital Rotterdam (F.G.A.M.), and the Department of Trials and Statistics, Daniel den Hoed Can-

sent unless paresis precluded their doing so, in which case oral consent was obtained.

Eligibility and Randomization

Patients were eligible if they fulfilled the criteria for acute Guillain–Barré syndrome,[23] were not able to walk 10 m independently, and could enter the study within two weeks of onset of the neuropathy. The criteria for exclusion were age of less than four years, a previous episode of Guillain–Barré syndrome, a previous severe allergic reaction to properly matched blood products, known selec-



of the disease, 74 of whom were randomly assigned to this treatment and 2 of whom received the treatment as a result of a protocol violation. Five incidents temporally related to the infusions were reported: a decline in blood pressure not necessitating any treatment (two patients) and dyspnea treated with a diuretic

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NEJM, 1992:326(17)

ICE Study: Significant Improvement in CIDP at 24 Weeks (Disability Scores, INCAT[a])

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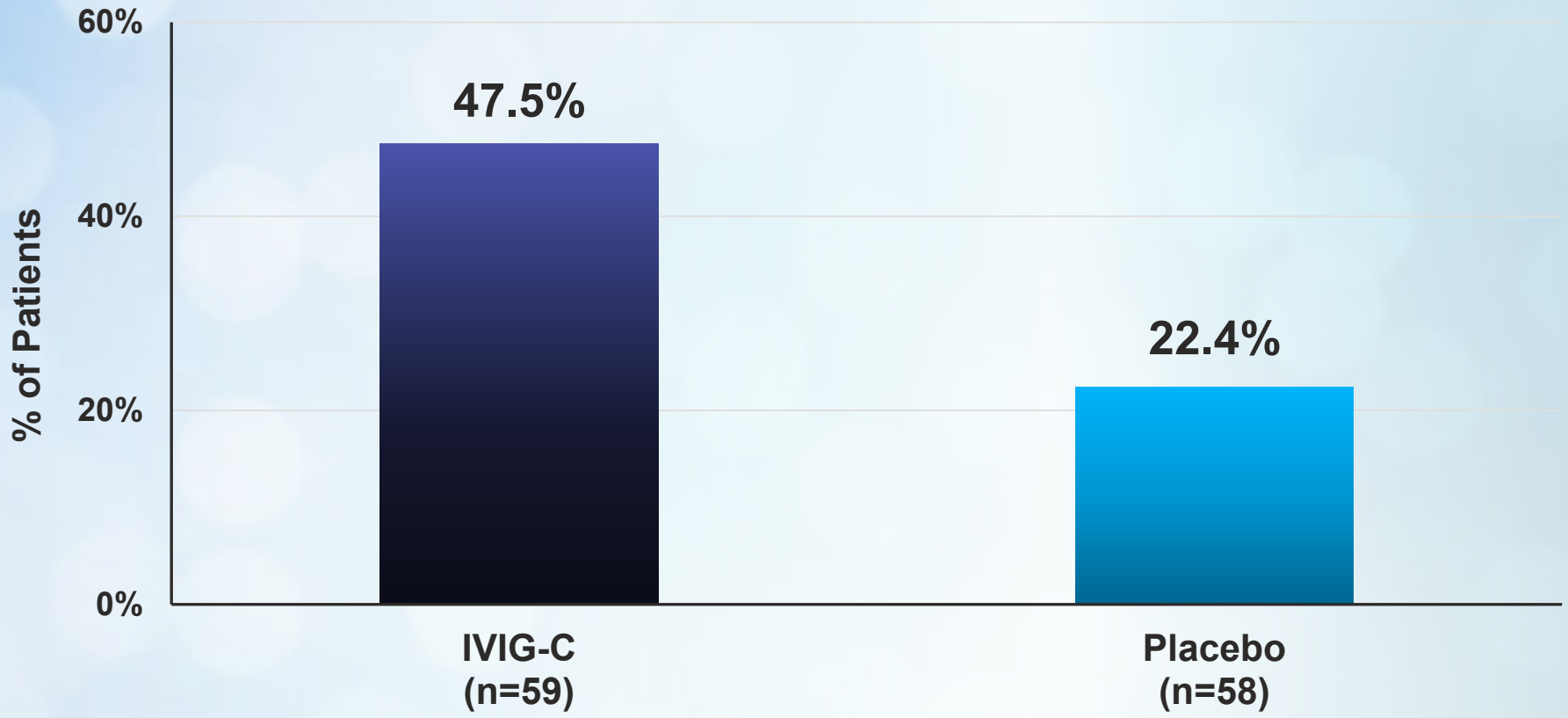

[a]Primary endpoint: Percentage of adjusted-INCAT responders who completed the initial treatment period without crossing over and maintained ≥1 point improvement through week 24.

INCAT, inflammatory neuropathy cause and treatment.

1. Hughes RAC. *Lancet Neurol.* 2008;7(2):136-144. **2.** Data on file, Grifols.

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IVIG in MMN

16 patients randomized to IVIg 0.4 g/kg/day for 5 days or placebo

Improvement assessed at 28 days

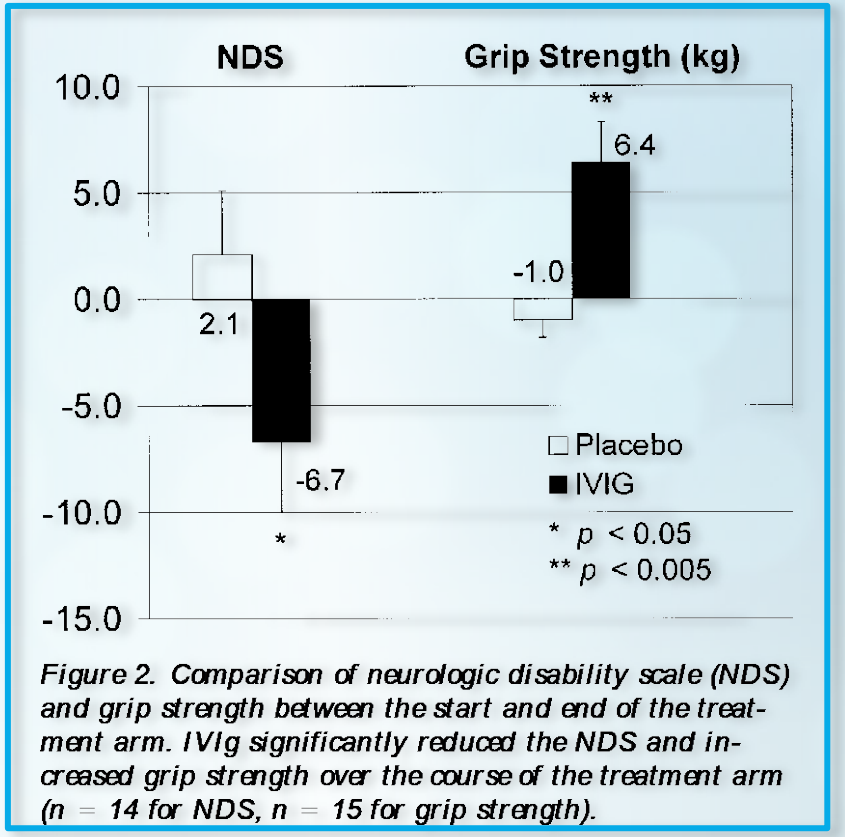


Figure 2. Comparison of neurologic disability scale (NDS) and grip strength between the start and end of the treatment arm. IVIg significantly reduced the NDS and increased grip strength over the course of the treatment arm (n = 14 for NDS, n = 15 for grip strength).

Frederico et al, Neurology 2000

IVIG in Dermatomyositis

95 pts with active DM randomized to 2 g/kg IVIg q 4 wks for 16 wks

Primary endpoint:
Total improvement score (TIS) of at least 20 with no worsening during 16 wks

TIS included:
Manual muscle test
Physician global assessment of disease activity
Patient global assessment of disease activity
Health assessment questionnaire
Extra muscular disease activity
Serum muscle enzyme levels

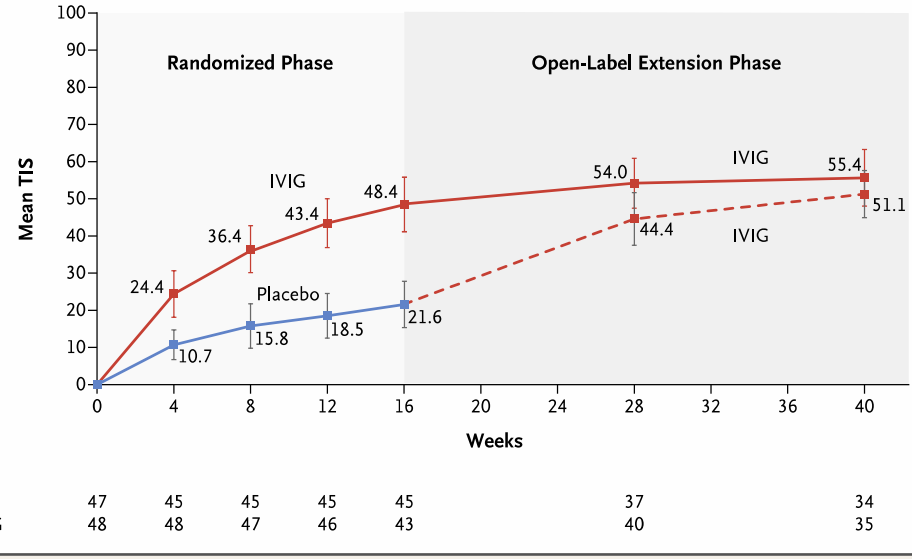


Figure 2. Total Improvement Score (TIS) at Week 16 and Week 40.
Shown is the mean TIS up to the end of the double-blind, randomized, placebo-controlled phase at week 16 and up to the end of the open-label extension phase at week 40. The TIS is a weighted composite score reflecting the change over time in a core set of six measures of myositis activity; scores range from 0 to 100, with higher scores indicating greater improvement (see the Supplementary Appendix). Conclusions cannot be drawn from the results from week 16 to week 40 (the open-label extension phase), because these results are descriptive only. I bars represent 95% confidence intervals.

IVIG in Myasthenia Gravis

IVIG for 36 weeks

Primary Endpoint:

≥50% reduction in corticosteroid dose at week 39

Figure 4 Kaplan-Meier Analysis of Probability of Myasthenia Gravis (MG) Worsening Over the Study Period

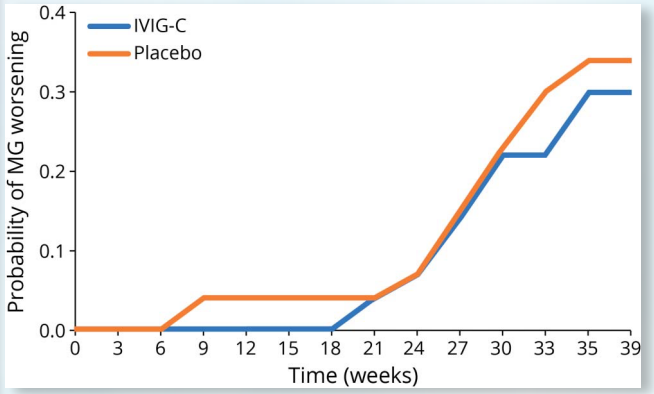
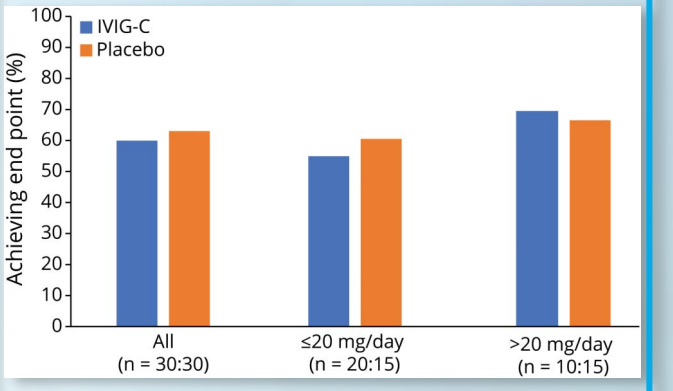
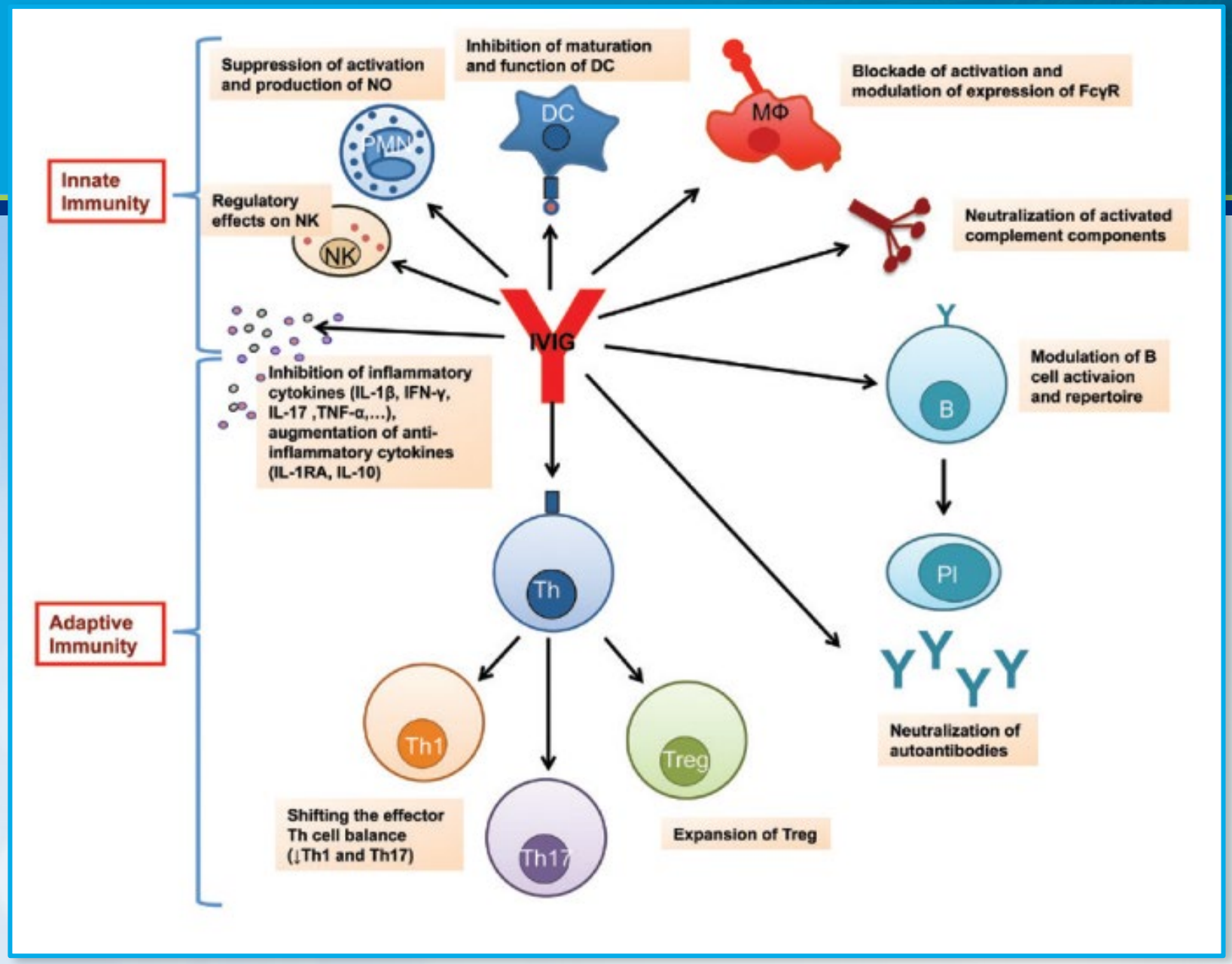


Figure 3 Percentage of Patients Achieving the Primary Efficacy End Point: 50% Reduction in Corticosteroid (CS) Dose



Patients were stratified according to whether entry CS dose was at or below the median (n = 20 IGIV-C; n = 15 placebo) or above the median baseline dose (20 mg prednisone equivalent) (n = 10 IGIV-C; n = 15 Placebo). There were no significant differences between the treatment groups overall. Subgroups illustrate that numerically in both arms, a higher percentage achieved primary end point if entering in the higher CS dose quantile. IGIV-C = immune globulin (human), 10% caprylate/chromatography purified; IVIG = IV immunoglobulin.

Bril et al, Neurology 2023



1. Bayry J, et al. 2021. 2. Bayry J, et al. JACI IP 2023

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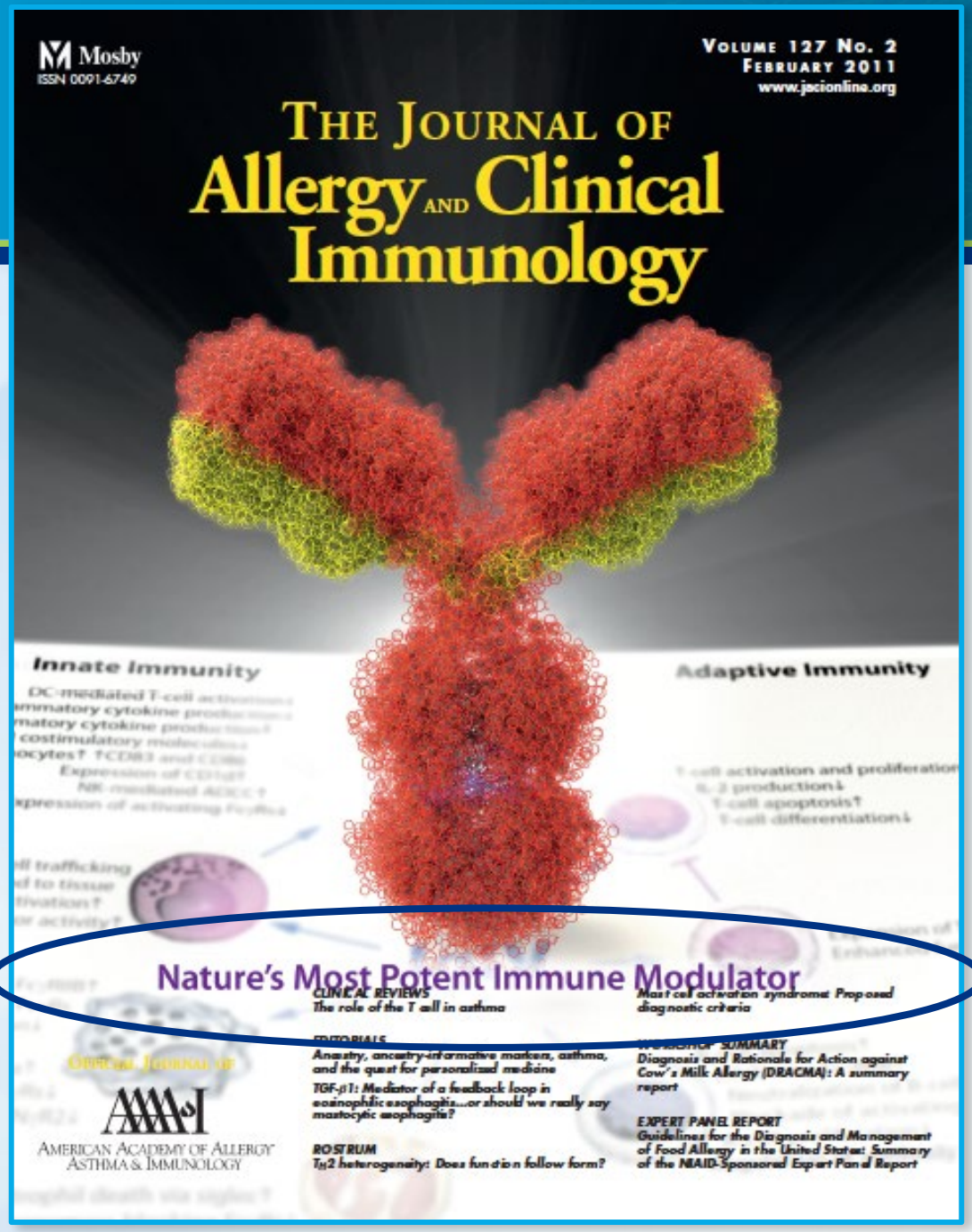

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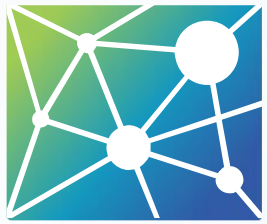

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