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Short Communication

IVIG efficacy in CIDP patients is not associated with terminal complement inhibition

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ABSTRACT

Patients with acute and chronic inflammatory demyelinating neuropathies exhibit elevated serum and cerebrospinal fluid (CSF) levels of terminal complement activation products and therapeutic inhibition of complement activation is currently tested for its safety and efficacy in patients with Guillain-Barré syndrome (GBS). Here, we determined serum levels of the complement activation products C3a, C5a and the soluble terminal complement complex (sTCC) in 39 individuals with chronic inflammatory demyelinating polyneuropathy (CIDP) who participated in one of the largest ever conducted clinical trial in patients with CIDP (ICE trial) and received Intravenous Immunoglobulin (IVIG) or placebo (albumin) in 3 week intervals for up to 24 weeks. In placebo-treated patients with spontaneous disease remission, serum sTCC levels moderately decreased over time. Levels of complement activation products were, however, not modulated by IVIG and remained unchanged in patients with a beneficial response to IVIG therapy as compared to those with steady or worsened disease. These results suggest that the therapeutic efficacy of IVIG in CIDP is based on immunomodulatory mechanisms different from complement inhibition. Terminal complement activation merits further investigation as a surrogate marker for disease progression and therapeutic target in patients with CIDP.

1. Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated disease of the peripheral nervous system and constitutes the most prevalent chronic autoimmune neuropathy (Dalakas and Medscape, 2011; Köller et al., 2005). The disease pathogenesis includes cell-mediated and humoral components. However, the prompt clinical efficacy of plasmapheresis suggests a critical role for a circulating factor in the disease mechanism.

We have previously shown that treatment-naïve patients with CIDP exhibit elevated serum and CSF levels of C5a and the soluble terminal complement complex (sTCC) (Quast et al., 2016). Increased systemic terminal complement activation correlated with clinical disease severity as defined by the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale (Quast et al., 2016). The anaphylatoxins C3a and C5a together with other complement components orchestrate proinflammatory responses both via complement receptor-mediated recruitment of myeloid subsets to areas of inflammation and through direct cellular damage by assembly of the terminal complement complex (TCC) (Morgan et al., 2017).

Intravenous immunoglobulin (IVIG) is a purified blood product preparation containing IgG antibodies from thousands of donors per lot and due to accelerated clinical improvement and less adverse effects compared to corticosteroids, high-dose administration of IVIG is considered as first-line therapy in the treatment of CIDP. One of the most comprehensively conducted randomized placebo-controlled clinical trials on IVIG in CIDP, termed the ICE trial, demonstrated that IVIG is safe and efficacious not only temporarily, but also in the long term (Hughes et al., 2008). IVIG can prevent complement-mediated tissue injury in a number of in vivo animal models of immune-mediated tissue injury (Basta et al., 1989; Magee et al., 1995) as well as in a human autoimmune myopathy (dermatomyositis) (Dalakas et al., 1993) and inhibits complement-mediated demyelination in vitro (Winter et al., 2016). Here, we examined terminal complement activation as a potential surrogate marker for clinical disease activity and response to IVIG therapy in patients with CIDP.

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2. Patients and methods

2.1. Patients

Patient serum samples from the randomized placebo-controlled *IGIV-C CIDP efficacy* (ICE) clinical study (Hughes et al., 2008) were analyzed. Patients with a diagnosis of CIDP (> 18 years old) and neuropathy-related relapsing or progressive sensory and motor dysfunction of one or more limbs (pre-existing at least for 2 months prior to study entry) and substantial disability reflected by an INCAT disability score of 2–9, were eligible to enter the study.

Upon screening, patients were randomly assigned to receive either 10% caprylate-chromatography purified immune globulin intravenous (IGIV-C; IVIG) (Gamunex, Talecris Biotherapeutics, Research Triangle Park, NC, USA) or 0.1% albumin. All patients received 2 g/kg body weight over 2–4 days and 1 g/kg body weight over 1–2 days thereafter in 3-week intervals for up to 24 weeks. All samples were collected between 2004 and 2005.

Upon venipuncture, samples were held at room temperature for 30 min to allow for clot retraction then centrifugation at 4 °C was performed and serum specimens were immediately frozen down at −80 °C. Beneficial response to IVIG treatment (remission) was specified as improving the clinical baseline score by ≥1 point in the adjusted INCAT disability score. This improvement had to be preserved through to the last clinical investigation in week 24. Patients were deemed non-responders (no remission) if their adjusted INCAT disability score increased by ≥1 point at any check-up after initial infusion of drug product, if patient score remained stable until week 6, or if their INCAT score improved but returned to baseline or below at any time at week 6 or afterwards, up to and including week 24 (Hughes et al., 2008).

2.2. ELISA

C5a, C3a and sTCC concentrations in patient samples were measured via ELISA (Tecomedical AG, Sissach, Switzerland) according to the manufacturer's recommendations.

2.3. Statistics

Complement component expression levels in patient samples were compared using the nonparametric two-tailed Mann–Whitney *U* test and two-tailed Wilcoxon signed rank test. A $p < .05$ was considered significant. All graphs and statistics were calculated and assembled using GraphPad Prism 5 (GraphPad Software, Inc.; La Jolla, CA).

3. Results

3.1. Levels of systemic complement activation products are stable over time in patients with CIDP

We analyzed baseline and post-treatment (24 weeks after initial treatment) serum specimens from 39 CIDP patients who had participated in the ICE trial, assessing the therapeutic effectiveness of IVIG in comparison to albumin (Hughes et al., 2008) (Table 1).

Upon activation, all complement pathways result in the cleavage of C3 into the active fragments C3a and C3b. C3b is progressively divided into iC3b, C3dg and C3d by Factor I, cofactors and unspecific proteases, allowing for interaction with specific C3 receptors that bind with high affinity to the respective fragments (Holers, 2014) (Ricklin et al., 2010). The activation of C3 is followed by the formation of the C5 convertase which cleaves C5 into C5a and C5b. The latter takes part in the assembly of the TCC, a pore-forming multipartite structure, which is made up of the complement factors C5b−C9.

The complement cascade conduces lytic cell death via incorporation of C5b-C9 into lipid bilayers. Soluble complex (sTCC) may be inhibited from membrane insertion via binding to regulatory factors such as clusterin (SP-40,40) or vitronectin (S protein) (Holers, 2014). Here, we determined serum levels of C3a, C5a and sTCC in patients with CIDP.

Table 1
Demographic characteristics of CIDP patients ($n = 39$).

	CIDP-IVIG	CIDP-Albumin
n	20	19
Female	11 (55%)	6 (32%)
Median age (years)	53	55
Age range (years)	19–75	18–74
Beneficial response to treatment[a]	12 (60%)	10 (52%)

[a] Defined by improvement in baseline disease severity by ≥1 point in the adjusted inflammatory neuropathy cause and treatment (INCAT) disability scale after week 24.

The mean serum concentration of all 39 CIDP patients was 45.39 µg/ml ± SD of 24.14 for C3a, 0.21 µg/ml ± SD of 0.08 for C5a and 15.24 µg/ml ± SD of 7.99 for sTCC which is in line with our previous investigations in an independent cohort of CIDP patients who showed increased serum concentrations of C5a (0.36 µg/ml ± SD of 0.12) and sTCC (7.04 µg/ml ± SD of 3.02) in comparison to non-inflammatory neurological disease control samples (0.05 µg/ml ± SD of 0.02 for C5a and 5.17 µg/ml ± SD of 1.71 for sTCC) (Quast et al., 2016).

Serum baseline levels of C3a, C5a, and sTCC were similar in patients later assigned to IVIG ($n = 20$) or placebo ($n = 19$) (Fig. 1A). We next determined whether serum levels of terminal complement activation components were regulated by IVIG. Analyzing paired samples of all CIDP patients before and 24 weeks after treatment with either IVIG or albumin, we detected no significant change in C3a, C5a, or sTCC serum levels in both, the IVIG or the placebo arm (Fig. 1B, C, D). Systemic terminal complement activation by virtue of C3a, C5a and sTCC serum concentrations, are therefore not modulated upon 24 weeks of IVIG treatment in patients with CIDP.

3.2. Beneficial response to IVIG therapy does not correlate with terminal complement activation in CIDP

Beneficial response to treatment was noted in 32 of 59 (54%) patients in the IVIG study arm and in 12 of 58 (21%) patients in the placebo group (Hughes et al., 2008). Therefore, we investigated whether the clinical response to IVIG or spontaneous disease remission in patients receiving placebo was associated with terminal complement inhibition.

In placebo-treated patients showing spontaneous disease remission, sTCC serum levels significantly decreased over time, but were not reflected by a similar decrease of C3a or C5a serum levels (Fig. 1E). No significant changes in serum C3a, C5a and sTCC levels were detected upon 24-week treatment in IVIG-treated CIDP patients who showed clinical improvement (Fig. 1F). In patients with a poor response to IVIG and placebo treatment, serum levels of all terminal complement activation components tested, remained unchanged over 24 weeks (Fig. 1G, H). Moreover, neither absolute values of C3a, C5a and sTCC serum levels nor relative changes (data not shown) in patients improving over 24 weeks of either IVIG or placebo treatment, were significantly different from those observed in individuals with stable or worsened disease.

4. Discussion

Deposition of complement component C3d on Schwann cells and compact myelin in patient-derived biopsies was the first indication of a potential pathogenic role of complement activation in the disease mechanism during CIDP (Dalakas and Engel, 1980; Hays et al., 1988). In patients with GBS, where membrane-bound TCC components are found to be deposited on Schwann cells (Hafer-Macko et al., 1996; Koski et al.,

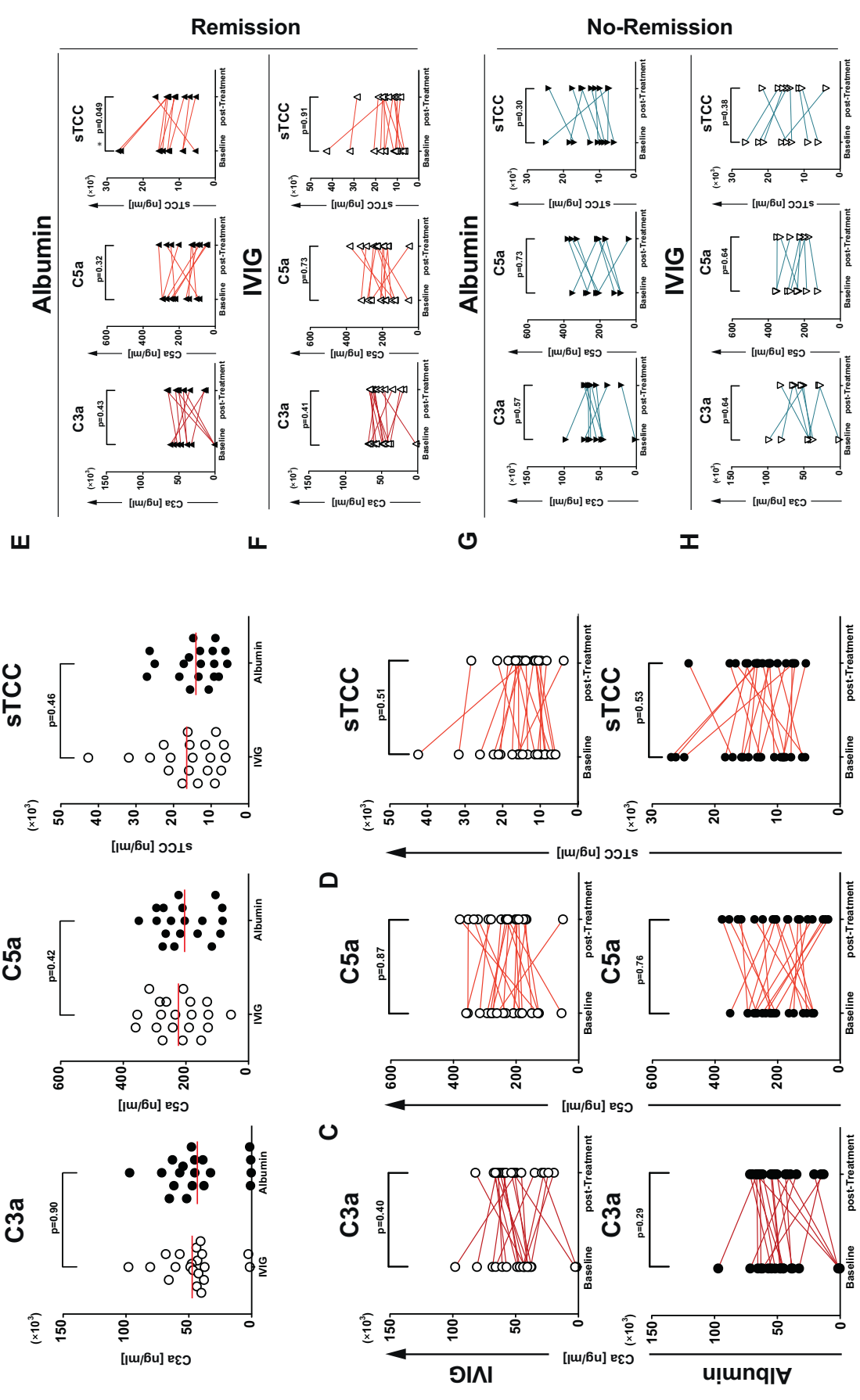

Fig. 1. Regulation of serum C3a, sTCC and C5a levels in patients with CIDP over time. (A) Baseline levels of complement factors in CIDP patients stratified into IVIG- or albumin-treated groups. Shown are serum levels of C3a, sTCC and C5a at the time point of screening (i.e. before treatment initiation). Each dot represents one individual patient. Treatment with IVIG or albumin does not significantly change C3a (B), C5a (C) or sTCC (D) serum levels after 24 weeks. Two dots connected by a line represent one individual patient at time point of screening (baseline) and after 24 weeks of treatment (post-Treatment). (E) In placebo-treated patients showing spontaneous disease remission after an observation period of 24 weeks, sTCC serum levels significantly decreased over time. (F) In IVIG-treated CIDP patients with a beneficial clinical response upon 24 weeks treatment, serum C3a, C5a and sTCC, levels were similar to baseline levels. (G, H) In patients with stable or worsened disease upon placebo or IVIG treatment, serum levels of terminal complement activation components remained unchanged over 24 weeks. Two dots connected by a line represent one individual patient at time point of screening (baseline) and after 24 weeks of treatment (post-Treatment). Statistics: Mann-Whitney *U* test (A) and Wilcoxon signed rank test (B-H). sTCC, soluble terminal complement complex; IVIG, intravenous immunoglobulin.

1987), serum TCC levels were shown to be increased as compared to healthy individuals and to decline with clinical improvement (Koski et al., 1987). In patients with CIDP, increased serum levels of terminal complement activation components, are reported to correlate with clinical disease severity (Quast et al., 2016). In line with these findings, serum sTCC levels decreased over time in patients with spontaneous disease remission. However, baseline and follow-up C3a, C5a and sTCC serum levels in IVIG-treated patients improving over 24 weeks did not differ from those determined in patients with steady or worsening disease indicating that the clinical response to IVIG therapy in CIDP patients is not reflected by inhibition of systemic complement activation.

Several modes of action have been suggested to mediate the anti-inflammatory activity of IVIG, including idiotypic antibodies, complement or by modulating Fc-gamma receptors (FcγRs) (Lünemann et al., 2015). While complement-inhibiting functions of IVIG were attributed to $F(ab')_2$ fragments from IVIG preparations, i.e. anti-idiotypic antibodies binding to complement products (Basta et al., 1989, 2003), most studies that employed suitable in vivo models of autoimmune diseases indicate that the IgG Fc fragment is the predominant mediator of the clinical efficacy of IVIG (Anthony et al., 2008; Bruhns et al., 2009; 2003; Kaneko et al., 2006a, 2006b; Samuelsson et al., 2001). IgG antibodies can regulate inflammatory responses through cross-linking cellular FcγRs. Most innate immune cells coexpress members of the FcγR group consisting of the activating FcγRIA, IIA, IIC, and IIIA and the inhibitory FcγRIIB. Circulating B cells and myeloid cells isolated from CIDP patients exhibit decreased surface expression of the inhibitory FcγRIIB while expression of activating FcγRs is enhanced (Quast et al., 2015; Tackenberg et al., 2009). Upregulation of the inhibitory FcγRIIB on macrophages and augmented infiltration of FcγRIIB-expressing myeloid cells to sites of inflammation in vivo was also observed following clinically effective IVIG treatment in several animal models of autoimmune diseases (Bruhns et al., 2003; Kaneko et al., 2006b; Samuelsson et al., 2001) supporting the hypothesis that restitution of the misdirected FcγR expression profile mediates in part the therapeutic effect of IVIG in CIDP patients.

There are limitations to our study. First, we investigated a relatively small number of patients and analyzed 2 timepoints only (pre- and post-treatment) but these patients were carefully characterized and followed over time in a placebo-controlled study (Hughes et al., 2008). Our data supports the notion that sTCC serum levels could potentially aid in monitoring disease activity but this warrants validation in independent cohorts of larger size. Secondly, our finding that IVIG efficacy in CIDP patients is not reflected by systemic complement inhibition does not exclude the possibility that IVIG modulates complement activation within the endoneurial compartment. However, a subgroup of CIDP patients with CD59 deficiency that allows complement/membrane attack complex (MAC)-mediated injury, was recently reported to not fully respond to IVIG but to require therapeutic inhibition of terminal complement activation with the monoclonal antibody eculizumab for complete remission (Mevorach et al., 2016), supporting the concept that IVIG-mediated protection in immune neuropathies can be complement-independent. Thirdly, we did not investigate as to which degree free C3b is depleted through covalent binding to IVIG. Our data in CIDP patients certainly do not exclude that the clinical efficacy of IVIG is mediated through terminal complement inhibition in other IVIG-responsive diseases. Indeed, in patients with dermatomyositis, clinically effective high-dose IVIG treatment was shown to inhibit endomysial deposition of activated complement fragments in situ and to reduce increased serum sTCC levels (Basta and Dalakas, 1994; Dalakas et al., 1993).

C5 convertase-mediated cleavage of C5 into C5a and C5b can be blocked by the recombinant humanized monoclonal antibody eculizumab, resulting in terminal complement inhibition (Rother et al., 2007). The clinical efficacy of eculizumab in patients with multifocal motor neuropathy has been investigated in an open label clinical study. 90% of patients who additionally also received IVIG preparations, continued to require IVIG treatment upon termination of the study, thus supporting the notion that mechanisms independent of terminal complement inhibition contribute to IVIG-mediated treatment effects (Fitzpatrick et al., 2011).

While we did not find evidence that the beneficial response to IVIG in CIDP patients is reflected by systemic complement inhibition, our data clearly do not exclude the possibility that inhibition of complement components might have a therapeutic merit in CIDP. Results from the ongoing Phase II clinical study testing the safety and efficacy of eculizumab in patients with GBS (Davidson et al., 2017; Yamaguchi et al., 2016) may be illuminating in assessing at a later time whether this drug may be also of relevance as a combination therapy with IVIG in patients with CIDP.

Disclosure

The authors declare that there is no conflict of interest.

Author contributions

Christian W. Keller: study concept and design, acquisition of data, analysis and interpretation, writing of the manuscript.

Isaak Quast: study concept and design.

Marinos C. Dalakas: study concept and design, analysis and interpretation, writing of the manuscript.

Jan D. Lünemann: study concept and design, analysis and interpretation, writing of the manuscript, study supervision.

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References

Anthony, R.M., Nimmerjahn, F., Ashline, D.J., Reinhold, V.N., Paulson, J.C., Ravetch, J.V., 2008. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG fc. Science 320, 373–376. https://doi.org/10.1126/science.1154315.

Basta, M., Dalakas, M.C., 1994. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. J. Clin. Invest. 94, 1729–1735. https://doi.org/10.1172/JCI117520.

Basta, M., Kirshbom, P., Frank, M.M., Fries, L.F., 1989. Mechanism of therapeutic effect of high-dose intravenous immunoglobulin. Attenuation of acute, complement-dependent immune damage in a Guinea pig model. J. Clin. Invest. 84, 1974–1981. https://doi.org/10.1172/JCI114387.

Basta, M., Van Goor, F., Luccioli, S., Billings, E.M., Vortmeyer, A.O., Baranyi, L., Szebeni, J., Alving, C.R., Carroll, M.C., Berkower, I., Stojilkovic, S.S., Metcalfe, D.D., 2003. F(ab)'2-mediated neutralization of C3a and C5a anaphylatoxins: a novel effector function of immunoglobulins. Nat. Med. 9, 431–438. https://doi.org/10.1038/nm836.

Bruhns, P., Samuelsson, A., Pollard, J.W., Ravetch, J.V., 2003. Colony-stimulating factor-1-dependent macrophages are responsible for IVIG protection in antibody-induced autoimmune disease. Immunity 18, 573–581.

Bruhns, P., Iannascoli, B., England, P., Mancardi, D.A., Fernandez, N., Jorieux, S., Daëron, M., 2009. Specificity and affinity of human Fcgamma receptors and their polymorphic variants for human IgG subclasses. Blood 113, 3716–3725. https://doi.org/10.1182/blood-2008-09-179754.

Dalakas, M.C., Engel, W.K., 1980. Immunoglobulin and complement deposits in nerves of patients with chronic relapsing polyneuropathy. Arch. Neurol. 37, 637–640.

Dalakas, M.C., Medscape, 2011. Advances in the diagnosis, pathogenesis and treatment of CIDP. Nat. Rev. Neurol. 7, 507–517. https://doi.org/10.1038/nrneurol.2011.121.

Dalakas, M.C., Illa, I., Dambrosia, J.M., Soueidan, S.A., Stein, D.P., Otero, C., Dinsmore, S.T., McCrosky, S., 1993. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N. Engl. J. Med. 329, 1993–2000. https://doi.org/10.1056/NEJM199312303292704.

Davidson, A.I., Halstead, S.K., Goodfellow, J.A., Chavada, G., Mallik, A., Overell, J., Lunn, M.P., McConnachie, A., van Doorn, P., Willison, H.J., 2017. Inhibition of complement in Guillain-Barré syndrome: the ICA-GBS study. J. Peripher. Nerv. Syst. 22, 4–12. https://doi.org/10.1111/jns.12194.

Fitzpatrick, A.M., Mann, C.A., Barry, S., Brennan, K., Overell, J.R., Willison, H.J., 2011. An open label clinical trial of complement inhibition in multifocal motor neuropathy. J. Peripher. Nerv. Syst. 16, 84–91. https://doi.org/10.1111/j.1529-8027.2011.00328.x.

Hafer-Macko, C.E., Sheikh, K.A., Li, C.Y., Ho, T.W., Cornblath, D.R., McKhann, G.M., Asbury, A.K., Griffin, J.W., 1996. Immune attack on the Schwann cell surface in acute inflammatory demyelinating polyneuropathy. Ann. Neurol. 39, 625–635. https://doi.org/10.1002/ana.410390512.

Hays, A.P., Lee, S.S., Latov, N., 1988. Immune reactive C3d on the surface of myelin sheaths in neuropathy. J. Neuroimmunol. 18, 231–244.

Holers, V.M., 2014. Complement and its receptors: new insights into human disease. Annu. Rev. Immunol. 32, 433–459. https://doi.org/10.1146/annurev-immunol-032713-120154.

Hughes, R.A.C., Donofrio, P., Bril, V., Dalakas, M.C., Deng, C., Hanna, K., Hartung, H.-P., Latov, N., Merkies, I.S.J., van Doorn, P.A., ICE Study Group, 2008. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol. 7, 136–144. https://doi.org/10.1016/S1474-4422(07)70329-0.

Kaneko, Y., Nimmerjahn, F., Madaio, M.P., Ravetch, J.V., 2006a. Pathology and protection in nephrotoxic nephritis is determined by selective engagement of specific fc receptors. J. Exp. Med. 203, 789–797. https://doi.org/10.1084/jem.20051900.

Kaneko, Y., Nimmerjahn, F., Ravetch, J.V., 2006b. Anti-inflammatory activity of immunoglobulin G resulting from fc sialylation. Science 313, 670–673. https://doi.org/10.1126/science.1129594.

Köller, H., Kieseier, B.C., Jander, S., Hartung, H.-P., 2005. Chronic inflammatory demyelinating polyneuropathy. N. Engl. J. Med. 352, 1343–1356. https://doi.org/10.1056/NEJMra041347.

Koski, C.L., Sanders, M.E., Swoveland, P.T., Lawley, T.J., Shin, M.L., Frank, M.M., Joiner, K.A., 1987. Activation of terminal components of complement in patients with Guillain-Barré syndrome and other demyelinating neuropathies. J. Clin. Invest. 80, 1492–1497. https://doi.org/10.1172/JCI113231.

Lünemann, J.D., Nimmerjahn, F., Dalakas, M.C., 2015. Intravenous immunoglobulin in neurology—mode of action and clinical efficacy. Nat. Rev. Neurol. 11, 80–89. https://doi.org/10.1038/nrneurol.2014.253.

Magee, J.C., Collins, B.H., Harland, R.C., Lindman, B.J., Bollinger, R.R., Frank, M.M., Platt, J.L., 1995. Immunoglobulin prevents complement-mediated hyperacute rejection in swine-to-primate xenotransplantation. J. Clin. Invest. 96, 2404–2412. https://doi.org/10.1172/JCI118297.

Mevorach, D., Reiner, I., Grau, A., Ilan, U., Berkun, Y., Ta-Shma, A., Elpeleg, O., Shorer, Z., Edvardson, S., Tabib, A., 2016. Therapy with eculizumab for patients with CD59 p.Cys89Tyr mutation. Ann. Neurol. 80, 708–717. https://doi.org/10.1002/ana.24770.

Morgan, B.P., Boyd, C., Bubeck, D., 2017. Molecular cell biology of complement membrane attack. Semin. Cell Dev. Biol. 72, 124–132. https://doi.org/10.1016/j.semcdb.2017.06.009.

Quast, I., Cueni, F., Nimmerjahn, F., Tackenberg, B., Lünemann, J.D., 2015. Deregulated Fcγ receptor expression in patients with CIDP. Neurol. Neuroimmunol. Neuroinflamm. 2, e148. https://doi.org/10.1212/NXI.0000000000000148.

Quast, I., Keller, C.W., Hiepe, F., Tackenberg, B., Lünemann, J.D., 2016. Terminal complement activation is increased and associated with disease severity in CIDP. Ann. Clin. Transl. Neurol. 3, 730–735. https://doi.org/10.1002/acn3.331.

Ricklin, D., Hajishengallis, G., Yang, K., Lambris, J.D., 2010. Complement: a key system for immune surveillance and homeostasis. Nat. Immunol. 11, 785–797. https://doi.org/10.1038/ni.1923.

Rother, R.P., Rollins, S.A., Mojcik, C.F., Brodsky, R.A., Bell, L., 2007. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Nat. Biotechnol. 25, 1256–1264. https://doi.org/10.1038/nbt1344.

Samuelsson, A., Towers, T.L., Ravetch, J.V., 2001. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science 291, 484–486. https://doi.org/10.1126/science.291.5503.484.

Tackenberg, B., Jelcic, I., Baerenwaldt, A., Oertel, W.H., Sommer, N., Nimmerjahn, F., Lünemann, J.D., 2009. Impaired inhibitory Fcgamma receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. Proc. Natl. Acad. Sci. U. S. A. 106, 4788–4792. https://doi.org/10.1073/pnas.0807319106.

Winter, M., Baksmeier, C., Steckel, J., Barman, S., Malviya, M., Harrer-Kuster, M., Hartung, H.-P., Goebels, N., 2016. Dose-dependent inhibition of demyelination and microglia activation by IVIG. Ann. Clin. Transl. Neurol. 3, 828–843. https://doi.org/10.1002/acn3.326.

Yamaguchi, N., Misawa, S., Sato, Y., Nagashima, K., Katayama, K., Sekiguchi, Y., Iwai, Y., Amino, H., Suichi, T., Yokota, T., Nishida, Y., Kohara, N., Hirata, K., Nishiyama, K., Yabe, I., Kaida, K.-I., Suzuki, N., Nodera, H., Tsuji, S., Koike, H., Kira, J.-I., Hanaoka, H., Kusunoki, S., Kuwabara, S., JET-GBS Group, 2016. A prospective, multicenter, randomized phase II study to evaluate the efficacy and safety of Eculizumab in patients with Guillain-Barré syndrome (GBS): protocol of Japanese Eculizumab trial for GBS (JET-GBS). JMIR Res. Protoc. 5, e210. https://doi.org/10.2196/resprot.6610.