Clinical Immunology (2010) 137, 21–30

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies

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Received 25 April 2010; accepted with revision 23 June 2010
Available online 1 August 2010

KEYWORDS
Intravenous immunoglobulin;
IVIG;
Trough concentration;
Dose;
Pneumonia;
Incidence;
Primary immunodeficiency;
Common variable immunodeficiency;
X-linked agammaglobulinemia;
Meta-analysis

Abstract Primary immunodeficiency disease (PIDD) associated with hypogammaglobulinemia is typically treated with immunoglobulin replacement therapy. When administered as intravenous immunoglobulin (IVIG), an IgG trough occurs prior to the next replacement dose. While frequently measured, IgG trough levels required to minimize infection risk are not established. To address this question, all available studies evaluating trough IgG and pneumonia incidence in PIDD patients with hypogammaglobulinemia receiving IVIG were quantitatively combined by meta-analysis. Seventeen studies with 676 total patients and 2,127 patient-years of follow-up were included. Pneumonia incidence declined by 27% with each 100 mg/dL increment in trough IgG (incidence rate ratio, 0.726; 95% confidence interval, 0.658–0.801). Pneumonia incidence with maintenance of 500 mg/dL IgG trough levels (0.113 cases per patient-year) was 5-fold that with 1000 mg/dL (0.023 cases per patient-year). This meta-analysis provides evidence that pneumonia risk can be progressively reduced by higher trough IgG levels up to at least 1000 mg/dL.

Introduction

Replacement therapy with IgG is an essential intervention in many primary immunodeficiency diseases (PIDDs) associated with humoral defects [1]. Continual IgG replacement therapy for patients with these types of PIDD reduces the frequency and severity of infections and can lessen morbidity and mortality [2]. The introduction of intravenous immunoglobulin (IVIG) allowed the administration of higher IgG doses than had been possible previously via the intramuscular route. When IVIG therapy was initially approved for clinical use, the recommended replacement dose was 100–200 mg/kg, but this has increased over subsequent decades in light of evolving clinical

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doi:10.1016/j.clim.2010.06.012

experience [1,3] as studies have shown less frequent bacterial infection and improved outcome with higher doses [4–9]. Doses of IVIG are most commonly provided at monthly intervals [10].

Administration of IVIG results in a rapid peak concentration that decreases over time before the next infusion. The serum IgG concentration immediately preceding the next scheduled IVIG infusion is designated the trough level and is viewed by a majority of immunologists as an important guide to therapy [10]. Trough levels have even been used as a means to evaluate the adequacy of a particular dosage [1,11]. While sufficient trough levels needed for optimal protection of PIDD patients against serious bacterial infections have yet to be established [12], a trough level of 500 mg/dL has in recent years been considered a minimum trough target [3–8,10]. The extent to which trough levels exceeding 500 mg/dL might confer additional benefit has been debated [1]. Resolution of this question has been hampered by the limitations of pertinent clinical data. Since PIDD is rare, the size of reported individual clinical studies has of necessity been small, thus limiting statistical power. Furthermore, different studies assessed disparate infection endpoints, such as total infections, serious bacterial infections or individual infection types. The range of trough levels reported in the individual studies has also often been restricted.

Meta-analysis can allow some of the limitations in existing data to be overcome. By quantitatively combining results from multiple small studies, meta-analysis can increase statistical power and potentially expand the range of trough levels over which infection incidence can be evaluated. A meta-analysis delineating the relationship between trough IgG level and infection incidence during IVIG therapy has not been previously published. Ideally, the primary endpoint for such a meta-analysis would be homogeneous and clinically relevant, with ample event rate data available over a wide range of associated trough levels. Pneumonia fulfills these criteria in patients with PIDD and is one of the primary validated serious bacterial infections used to determine the efficacy of immunoglobulin replacement therapies (www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm072130.htm).[1]

Pneumonia is among the most frequent manifestations of PIDD [13,14]. Between 75 and 84% of patients with common variable immunodeficiency (CVID) were found to have experienced at least one episode of pneumonia before diagnosis, and many had experienced multiple prior episodes [15]. In the US patient registry of X-linked agammaglobulinemia (XLA), 62% of patients had experienced pneumonia [16]. A high pneumonia incidence has also been reported in other PIDDs affecting humoral immunity, including the X-linked hyper-IgM syndrome (81%) [17], NEMO deficiency (31%) [18] and the Wiskott–Aldrich syndrome (45%) [19].

In PIDD patients pneumonia can be severe, frequently requiring intravenous antibiotics and/or hospitalization [20]. Some clinical studies have focused solely on the efficacy of IVIG in preventing pneumonia [21–23], while other studies without such a narrow focus have nevertheless reported pneumonia incidence [4–6,24,25]. Furthermore, pneumonia incidence has been reported for a broad range of trough levels [14,24]. This meta-analysis demonstrates statistically significant progressive decreases in pneumonia incidence associated with trough IgG increases in PIDD patients with antibody deficiency.

[1] This weblink was valid as of July 2010.

Methods

Study selection

Eligible clinical studies must have furnished data on pneumonia incidence in relation to IgG levels among patients receiving IVIG therapy for PIDD with antibody deficiency. Investigations exclusively or predominantly dealing with IgG subclass deficiency or specific antibody deficiency were not eligible. Studies of IgG treatment exclusively via the intramuscular or subcutaneous routes were excluded since these routes of dosing result in a distinct kinetics without comparable trough levels [26]. When more than one route of administration was investigated, only the data pertaining to IVIG were used. No restrictions were placed on study design, time period or reporting language. Final publication was not required, and completed but unpublished studies were sought, for example, through searches of ClinicalTrials.gov. However, studies reported exclusively in abstract form were not sought or included.

Search strategy

Eligible studies were identified by computer searches of MEDLINE and the Cochrane Library. The searches were conducted between May and September, 2009. Search terms included IVIG; IGIV; intravenous immune globulin; intravenous immunoglobulin; Carimune; Endobulin; Flebogamma; Gamimune; Gammagard; Gammaglobulin; Gammaplex; Gamunex; Intraglobin; Iveegam; Nordimmune; Octagam; Polygam; Privigen; Sandoglobulin; Vigam; primary immunodeficiency; hypogammaglobulinemia; common variable immunodeficiency; agammaglobulinemia; X-linked agammaglobulinemia; and hyper-IgM syndrome. Reference lists of primary study publications and review articles were also examined.

Data extraction

Two investigators independently determined study eligibility and extracted data from the eligible study reports. The κ statistic was 0.68 with a 95% confidence interval (CI) of 0.49–0.86, indicating a high degree of inter-rater agreement. Differences in interpretation were resolved through the intermediation of a third investigator. Data were extracted on study design; geographic study region; IVIG product or supplier; number of patients; mean patient age; gender distribution; clinical diagnosis; numbers of pneumonia episodes; duration of study observation period; IVIG dose and treatment interval; and trough IgG level. In some studies [4–6,22], individual patient trough IgG values were presented as graphical displays in the study reports. Those data were captured from the displays by computer digitization to a precision of ±0.001 mg/dL.

Statistical analysis

Data were analyzed using R version 2.7.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria). The relationships between pneumonia incidence and either trough IgG or IVIG dose were analyzed by