Hypogammaglobulinemia: therapeutic rationale

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Hypogammaglobulinemia is a feature of several B-cell disorders and is manifested clinically by recurrent infection, most commonly chronic upper and lower respiratory tract disease. Immunoglobulin replacement therapy is available, with at least four different routes of administration. There are as yet no convincing data that allow comparison of the cost-effectiveness of these methods. However, by individualizing therapy for each patient, it is possible to prevent life-threatening acute infections, reduce the severity of chronic upper and lower respiratory tract disease, improve pulmonary function and achieve normal levels of IgG. These are the currently acceptable goals of therapy in patients with hypogammaglobulinemia.

Dans plusieurs maladies B-lymphocytaires il existe une hypogammaglobulinémie qui se manifeste cliniquement par l'infection récidivante, surtout des voies respiratoires hautes et basses. La thérapeutique de remplacement des immunoglobulines peut se faire par quatre voies différentes dont on ne connaît pas de façon certaine la rentabilité relative. Le traitement adapté à chaque malade permet de lui épargner des infections aiguës comportant un risque de mort, d'abaisser chez lui la gravité de l'infection chronique des voies respiratoires hautes et basses, d'améliorer sa fonction pulmonaire et de lui assurer une concentration sanguine normale d'IgG. On s'accorde actuellement à voir là les buts de cette thérapeutique.

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Humoral immunodeficiency states, excluding isolated IgA deficiency, account for 17.4%, 36%, 37.9% and 50% of all immunodeficiency diseases in Italy, Sweden, Japan and the United States respectively.[1] Available estimates from national surveys suggest the following incidence rates of hypogammaglobulinemia per 100 000 population: 0.2 in Denmark,[2] 1.0 in the United Kingdom[3] and 2.0 in Sweden.[4] In contrast, Japanese investigators have reported an incidence rate of 0.5 per million.[5]

X-linked agammaglobulinemia, or Bruton's agammaglobulinemia, is a disorder in which there is virtual absence of serum immunoglobulins* of all classes (panhypogammaglobulinemia) and an inability to make antibodies. The identifying clinical characteristic is recurrent pyogenic infections starting in infancy or early childhood, only males being affected. The absence of mature B cells or plasma cells implies a maturation block in pre-B-cell to B-cell differentiation; clinically one finds hypoplasia of the adenoids, tonsils and peripheral lymph nodes.[7-9] In contrast, common variable immunodeficiency, or acquired hypogammaglobulinemia, is characterized by variably low levels of serum immunoglobulins and variably increased susceptibility to infection.[7] The patients usually present in the second or third decade of life. B cells are usually present in the circulation, but immunoglobulin production is impaired.[1,2] The serum level of IgG is characteristically below 2.00

**In an attempt to minimize confusion, we will use the term immunoglobulin when referring to the antibody-containing fraction of human serum, as recommended by the World Health Organization.[6] Previously used terms include gammaglobulin, immune globulin and immune serum globulin. The last term will be reserved specifically for the Cohn fraction II preparation used for intramuscular replacement therapy.*

g/L, and the levels of IgA and IgM are typically below 0.50 g/L.[8]

Therapeutic options

Intramuscular administration of immune serum globulin

The nature of the basic biologic defect in most humoral immunodeficiency states remains unknown. It is widely agreed that the designation "common variable immunodeficiency" encompasses a heterogeneous group of disorders.[7-9] Intrinsic B-cell defects[10] including failure of the cells to mature or to secrete immunoglobulin upon stimulation,[11] abnormalities of regulatory T cells,[12,13] serum inhibitors of B-cell differentiation[11] and even autoantibodies directed against T or B cells[14] have been documented in such patients. The wide spectrum of pathogenetic abnormalities in this disorder is mirrored in the heterogeneity of the clinical features of patients with common variable immunodeficiency. The most common presenting problems are bronchiectasis, recurrent pneumonia and recurrent upper respiratory tract infections, including sinusitis, otitis and pharyngitis. However, there are some patients with common variable immunodeficiency and profoundly depressed levels of serum immunoglobulins who appear to have only minimal susceptibility to infection and whose chief complaints are fatigue and malaise. If promptly treated with full dosages of appropriate antibiotics they appear to recover without incident from infections. The decision to treat these patients with immunoglobulin is empiric, as there are no guidelines in the literature for starting therapy.

Bruton's landmark description of agammaglobulinemia[15] and the confirmation by Janeway and colleagues[16] the following year of the efficacy of immune serum globulin treatment established the role of immunoglobulin therapy in these conditions. In 1966 Janeway and Rosen recommended empiric replacement therapy with immunoglobulin in patients with antibody deficiency syndromes.[17] Subsequently the British Medical Research Council Working-Party on Hypogammaglobulinaemia found evidence of a significant decrease in morbidity in patients receiving immune serum globulin and recommended a starting dosage of 25 mg/kg per week; if this provided inadequate control the dosage could be increased to 50 mg/kg per week.[3] For almost 30 years since, intramuscular injection of immune serum globulin at these dosages has been used in the treatment of humoral immunodeficiency states.[18]

Intramuscular administration of immune serum globulin is not without problems. Pain at the site of injection often lasts for long periods. Lack of muscle mass, especially in children, restricts the volume that can be administered. Consequently, more frequent injections have been used to achieve the prescribed monthly dosage. Peak levels may not be reached until up to 14 days after injection. Adverse reactions occur in 19% of patients, at an overall frequency rate of 1 in 400 injections;[3] reactions include hypotension, loss of consciousness, chest tightness, dyspnea and episodes of facial swelling.[5] These anaphylactoid reactions are thought to be a result of inadvertent intravenous uptake of immune serum globulin from the intramuscular injection site, with subsequent complement activation by aggregated IgG molecules.[18,19]

Subcutaneous administration of immune serum globulin

Subcutaneous administration of immune serum globulin with an automated infusion pump has been suggested to have advantages over the intramuscular route. Infusions are given over a 3- to 8-hour period at the patient's convenience, generally at home. They are well tolerated, with no adverse effects reported to date. Moreover, higher serum IgG levels and, by implication, better control can be achieved.[20-22] Cost analysis of this method of immunoglobulin replacement has shown that it compares favourably with the intramuscular route (unpublished data, 1984).

Plasma therapy

Plasma therapy as a means of immunoglobulin replacement enjoyed a vogue in the late 1960s.[23] A "buddy system", with one or two screened donors for each patient, was used to avoid the infective risks inherent in the use of pooled plasma. The need for admission to hospital every 3 to 4 weeks, the occurrence of anaphylactoid reactions and the theoretical concern that less extensive passive immunity would be conferred by the immunoglobulins contained in plasma from a smaller number of donors than by those in immune serum globulin, which is derived from plasma pools of 500 to 1000 patients, limited the popularity of this mode of treatment.

Intravenous administration of immunoglobulin

Because of the shortcomings of the three approaches to therapy outlined above, the main thrust of research in this area over the last 30 years has been the development of a preparation of immunoglobulin that is safe to administer intravenously — that is, a preparation devoid of the vasomotor phenomena associated with intravenous administration of immune serum globulin. Maneuvers that remove anticomplementary activity while retaining biologic efficacy have yielded several safe intravenous preparations of immunoglobulin.[24] The relative safety of these preparations (minor side effects occur in 5% to 10% of patients)

and the ability to obtain higher serum immunoglobulin levels in recipients have been well documented.[25-27] It has been reported that the severe anaphylactic reactions experienced by a few patients may be eliminated by premedication with corticosteroids.[28]

However, the few studies addressing the issue of increased efficacy of these intravenous preparations have provided inconclusive results. In a large cooperative study comparing intravenously given immunoglobulin and intramuscularly given immune serum globulin at identical dosages (100 mg/kg per month) with crossover, no significant difference in the number or prevalence of infections was noted.[29]

Nolte and colleagues[30] found significantly lower rates of infection with 150 mg/kg per month of immunoglobulin given intravenously than with 100 mg/kg per month given intramuscularly, and benefit was confirmed in the crossover arm of the study. This showed that a higher dosage of immunoglobulin results in clinical benefit, but it does not permit conclusions about the comparative efficacy of intravenous versus intramuscular administration.

Cunningham-Rundles and associates[31] compared 300 mg/kg per month given intravenously with 100 mg/kg per month given intramuscularly in 21 patients (19 with common variable immunodeficiency) and reported a substantial reduction in both acute specific illness and antibiotic requirements over 12 months. However, since prospective data on the high-dose intravenous therapy were compared with retrospective data on the conventional-dose intramuscular therapy, interpretation of the results is difficult, and the lack of randomization or blinding makes bias impossible to rule out. As in the paper by Nolte and colleagues the authors purported to show a clinical benefit with a higher dosage of immunoglobulin and, by implication, ascribed the benefit to the intravenous route. However, they did not show that 300 mg/kg per month given intravenously was better than 150 mg/kg per month given intravenously or better than the equivalent dosage given intramuscularly. Moreover, three other groups were unable to show that higher intravenous dosages of immunoglobulin were more effective than standard intramuscular therapy, even when the intravenous dose was tailored to match each patient's rate of degradation of infused immunoglobulin.[32-34]

Results of a recently reported randomized crossover study of 12 patients indicate that the patients receiving a maintenance dosage of intravenous immunoglobulin that kept the serum IgG level above 5.0 g/L had fewer acute infections and had improved pulmonary function.[35]

Goals of immunoglobulin replacement therapy

Failure to eliminate or decrease recurrent infections, especially respiratory tract infections, may mean that significant structural tissue damage has already occurred by the time therapy is begun.[3] This provides an additional, mechanical reason for infection in the airways, which generally does not respond to administration of antibody. Evidence from Sweden suggests an average delay of 12 years between onset of symptoms and institution of specific therapy in patients with common variable immunodeficiency.[4] Impairment of pulmonary function at the time of study was considerably more pronounced in patients for whom the start of immunoglobulin replacement therapy was delayed or in whom replacement was deemed inadequate. Perhaps, then, a stated aim of therapy in patients with common variable immunodeficiency should be the prevention of organ damage, in particular lung damage, which typically results in obstructive lung defects.

This issue has received little attention, but recent work from Roifman and coworkers[36] not only confirmed severe obstructive lung defects in patients with hypogammaglobulinemia but also clearly showed that, at least in a small, uncontrolled study, some degree of reversibility may be expected when high-dose intravenous immunoglobulin replacement therapy is used (600 mg/kg per month). This improvement in lung function was accompanied by virtual disappearance of pneumonia over the 12 months of study in the seven patients described.

It is clear that some patients benefit from a therapeutic approach that includes administration of immunoglobulin in excess of the conventional dosage of 100 mg/kg per month. The route of administration remains a problem, because high dosages preclude the use of the intramuscular route for some patients. Intravenous administration eliminates the problems associated with discomfort and hence compliance but has negative features, including adverse reactions and cost. The latter has seldom been addressed and until recently had never been formally studied. We performed a cost analysis of the four available methods of immunoglobulin replacement and found that the intramuscular and subcutaneous routes of administration are the least costly methods (unpublished data, 1984). The subcutaneous route appears to be highly attractive because it is much less expensive than the intravenous route and it permits administration of larger doses than the intramuscular method. Clearly, more studies on the effectiveness of this route of administration in patients whose disease is difficult to control are required.

Hypogammaglobulinemia and lymphoproliferative disorders

Acquired hypogammaglobulinemia is a recognized laboratory feature of lymphoproliferative disorders. In the chronic lymphocytic leukemias, for example, immunoglobulin levels (especially

IgG levels) appear to fall progressively,[37] and 6 years after diagnosis approximately 50% of surviving patients are hypogammaglobulinemic.[38] Similarly, in multiple myeloma, although the total immunoglobulin levels may not fall, owing to monoclonal gammopathy, impaired synthesis of functional polyclonal immunoglobulin is observed.[39] Furthermore, these immunoglobulin abnormalities are thought to be related to the incidence and severity of the infections in these patients.[40,41]

It is assumed that when recurrent or severe sepsis is a problem in these settings, immunoglobulin replacement therapy is indicated. The use of immunoglobulin prophylaxis in a small number of patients with chronic lymphatic leukemia suggests that it is well tolerated and has beneficial effects in the prevention of sepsis.[40,42,43] Uncontrolled studies in patients with multiple myeloma also indicate good tolerance of intravenously given immunoglobulin, and controlled efficacy studies of prophylaxis of infection are indicated.[44] An earlier controlled clinical trial of low dosages (less than 100 mg/kg) of gammaglobulin given intramuscularly to patients with myeloma showed no effect of treatment on the rate or type of infection.[45] However, since the patients were not stratified on the basis of immunoglobulin levels at the time of entry or effect of immunoglobulin therapy on circulating immunoglobulin levels, a beneficial effect of therapy in a select group of patients with extraordinary susceptibility to infection and profound hypogammaglobulinemia may have been overlooked. Although there is as yet no convincing evidence from properly controlled clinical trials that immunoglobulin replacement therapy is effective in the management of hypogammaglobulinemia associated with certain leukemias and myeloma, empiric administration in adequate dosages may be indicated in patients with recurrent infections that are difficult to manage.

Conclusions

As in clinical medicine generally, individualized therapy based on specific patient needs should be the approach to patients with recurrent infections due to hypogammaglobulinemia. We have successfully used the intramuscular, subcutaneous and intravenous routes for immunoglobulin replacement therapy. Patients largely prefer the last two routes for reasons of comfort and convenience. Adequate serum immunoglobulin levels appear to be the best guide to dosage and frequency of administration. If a less expensive intravenous product can be created, new developments in home self-administration[46,47] will make it the method of choice for immunoglobulin replacement therapy.

It is clear that hypogammaglobulinemia is a feature of a group of disorders that are heterogeneous at both a clinical and a basic biologic level. Some patients with common variable immunodeficiency who present clinically as adults appear to remain remarkably well without specific immunoglobulin replacement therapy. Indeed, a population of people with undiagnosed disease may exist who have not required medical attention. Against this background, and since there are no guidelines for starting therapy and the optimal dosage and route of administration are uncertain, it is imperative to clearly define the objectives of treatment. It is becoming apparent that these aims should include, from the outset, prevention or reversal of tissue damage, especially in the lungs. In contrast, the identifying clinical feature in X-linked agammaglobulinemia is recurrent infection with predominantly invasive extracellular pyogenic organisms. Diagnosis is made early in life, and immunoglobulin replacement therapy is often considered life-saving. Although in neither condition is the optimal dosage or the optimal frequency or rate of administration clearly established, the use of immunoglobulin appears to lead to a reduction in the frequency and severity of infection and improved results of simple pulmonary function tests.

References

1. Luzi G, Businco L, Aiuti F: A national registry for primary immunodeficiency syndromes in Italy: a report for the period 1972-1982. *Birth Defects* 1983; 19: 161-163
2. Koch C, Andersen V, Faiser V et al: Primaere immunodefekter I Danmark. *Ugeskr Laeger* 1981; 143: 2479-2484
3. Summary report of a British Medical Research Council working-party. Hypogammaglobulinaemia in the United Kingdom. *Lancet* 1969; 1: 163-168
4. Bjorkander J, Bake B, Hanson LA: Primary hypogammaglobulinaemia: impaired lung function and body growth with delayed diagnosis and inadequate treatment. *Eur J Respir Dis* 1984; 65: 529-536
5. Hayakawa H, Iwata T, Yata J et al: Primary immunodeficiency syndrome in Japan. I. Overview of a nationwide survey on primary immunodeficiency syndrome. *J Clin Immunol* 1981; 1: 31-39
6. IUIS/WHO notice: appropriate uses of human immunoglobulin in clinical practices. *Clin Exp Immunol* 1983; 1952: 417-422
7. Buckley RH: Immunodeficiency. *J Allergy Clin Immunol* 1983; 72: 627-641
8. Immunodeficiency. Report of a WHO scientific group. *Clin Immunol Immunopathol* 1979; 13: 296-359
9. Rosen FS, Cooper MD, Wedgewood RJP: The primary immunodeficiencies. *N Engl J Med* 1984; 311: 300-310
10. De La Concha G, Oldham G, Webster A et al: Quantitative measurement of T and B cell function in "variable" primary hypogammaglobulinemia: evidence for a consistent B-cell defect. *Clin Exp Immunol* 1977; 27: 208-215
11. Geha RS, Schneenberger E, Merler E et al: Heterogeneity of "acquired" or common variable agammaglobulinemia. *N Engl J Med* 1974; 291: 1-6
12. Waldmann TA, Broder S, Blaese RM et al: Role of suppressor T cells in pathogenesis of common variable hypogammaglobulinaemia. *Lancet* 1974; 2: 609-613
13. Reinherz EL, Rubinstein A, Geha RS et al: Abnormalities of immunoregulatory T cells in disorders of immune function. *N Engl J Med* 1979; 301: 1018-1022
14. Gelfand EW, Borel H, Berkel AI et al: Auto-immunosup-

pression: recurrent infections associated with immunologic unresponsiveness in the presence of an auto-antibody to IgG. *Clin Immunol Immunopathol* 1972; 1: 155-163
15. Bruton OC: Agammaglobulinemia. *Pediatrics* 1952; 9: 722-728
16. Janeway CA, Apt L, Gitlin D: Agammaglobulinemia. *Trans Assoc Am Physicians* 1953; 66: 200-201
17. Janeway CA, Rosen FS: The gammaglobulins. IV. Therapeutic uses of gammaglobulin. *N Engl J Med* 1966; 275: 826-831
18. Dwyer JM: Thirty years of supplying the missing link. History of gammaglobulin therapy for immunodeficient states. *Am J Med* 1984; 76 (suppl 3A): 46-52
19. Barandun S, Kistler P, Jeunet F et al: Intravenous administration of human gammaglobulin. *Vox Sang* 1962; 7: 157-174
20. Berger M, Cupps TR, Fauci AS: Immunoglobulin replacement therapy by slow subcutaneous infusion. *Ann Intern Med* 1980; 93: 55-56
21. Ugazio AG, Duse M, Re R et al: Subcutaneous infusion of gammaglobulins in management of agammaglobulinaemia [C]. *Lancet* 1982; 1: 226
22. Roord JJ, Van Der Meer JWM, Wietse K et al: Home treatment in patients with antibody deficiency by slow subcutaneous infusion of gamma globulin [C]. Ibid: 689-690
23. Stiehm ER, Vaerman JP, Fudenberg HH: Plasma infusions in immunologic deficiency states: metabolic and therapeutic studies. *Blood* 1966; 28: 918-937
24. Eibl M: Treatment of defects of humoral immunity. *Birth Defects* 1983; 19: 193-200
25. Rousell RH, Fox EN (eds): Intravenous immune globulin: its use and potential. *J Clin Immunol* 1982; 2 (suppl): 1S-48S
26. Wedgewood R, Rosen FS, Paul NW (eds): Primary immunodeficiency diseases. *Birth Defects* 1983; 19: 153-241
27. Good RA (ed): Intravenous immune globulin and the compromised host. *Am J Med* 1984; 76 (suppl 3A): 1-231
28. Lederman HM, Roifman CM, Lavi S et al: Corticosteroids for prevention of adverse reactions to intravenous immune serum globulin infusions in hypogammaglobulinemic patients. *Am J Med* 1986; 81: 443-446
29. Ammann AJ, Ashman RF, Buckley RH et al: Use of intravenous gammaglobulin in antibody immunodeficiency: results of a multicenter controlled trial. *Clin Immunol Immunopathol* 1982; 22: 60-67
30. Nolte MT, Pirofsky B, Gerritz GA et al: Intravenous immunoglobulin therapy for antibody deficiency. *Clin Exp Immunol* 1979; 36: 237-243
31. Cunningham-Rundles C, Siegal FP, Smithwick EM et al: Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. *Ann Intern Med* 1984; 101: 435-439
32. Ochs HD, Fischer SH, Wedgewood RJ et al: Comparison of high-dose and low-dose intravenous immunoglobulin therapy in patients with primary immunodeficiency diseases. *Am J Med* 1984; 76 (suppl 3A): 78-82
33. Sorensen RU, Polmar SH: Efficacy and safety of high dose intravenous immune globulin therapy for antibody deficiency syndromes. Ibid: 83-90
34. Schiff RI, Rudd C, Johnson R et al: Individualization of gammaglobulin dosage in patients with humoral immunodeficiency. *Birth Defects* 1983; 19: 209-212
35. Roifman CM, Levison H, Gelfand EW: High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. *Lancet* 1987; 1: 1075-1077
36. Roifman CM, Lederman HM, Lavi S et al: Benefit of intravenous IgG replacement in hypogammaglobulinemic patients with chronic sinopulmonary disease. *Am J Med* 1985; 79: 171-174
37. Hudson RP, Wilson SJ: Hypogammaglobulinemia and chronic lymphocytic leukemia. *J Clin Lab Med* 1957; 50: 829-830
38. Ben-Bassat I, Many A, Modan M et al: Serum immunoglobulin in chronic lymphatic leukemias. *Am J Med Sci* 1979; 278: 4-9
39. Broder S, Humphrey R, Durm M et al: Impaired synthesis of polyclonal (non-paraprotein) immunoglobulins by circulating lymphocytes from patients with multiple myeloma. *N Engl J Med* 1975; 293: 887-892
40. Shaw RK, Szwed C, Boggs DR et al: Infection and immunity in chronic lymphocytic leukemia. *Arch Intern Med* 1960; 106: 467-478
41. Gale RP, Foon KA: Chronic lymphocytic leukemia. Recent advances in biology and treatment. *Ann Intern Med* 1985; 103: 101-120
42. Besa EC: Use of intravenous immunoglobulin in chronic lymphocytic leukemia. *Am J Med* 1984; 76 (suppl 3A): 209-218
43. Huser HJ, Schwander D, Wegmann A et al: Tolerability and pharmacokinetics of an intravenous immunoglobulin preparation in immunologically normal subjects and tolerability in patients with hypogammaglobulinemia resulting from chronic lymphatic leukemia. *Schweiz Med Wochenschr* 1986; 116: 151-156
44. Gordon DS, Hearne EB, Spira TJ et al: Phase I study of intravenous gammaglobulin in multiple myeloma. *Am J Med* 1984; 76 (suppl 3A): 111-116
45. Salmon SE, Samal BA, Hayes DM et al: Role of gamma globulin for immunoprophylaxis in multiple myeloma. *N Engl J Med* 1967; 277: 1336-1340
46. Ashida ER, Saxon A: Home intravenous immunoglobulin therapy by self-administration. *J Clin Immunol* 1986; 6: 306-309
47. Ochs HD, Fischer SH, Lee ML et al: Intravenous immunoglobulin home treatment for patients with primary immunodeficiency diseases. *Lancet* 1986; 1: 610-611