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Therapeutic Strategies in Common Variable Immunodeficiency

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Abstract

The treatment of common variable immunodeficiency (CVID) is currently based on the early recognition of the condition and replacement immunoglobulin combined with prompt treatment of infections and complications. The route of administration, dose and frequency of administration of immunoglobulin still vary between centres and countries. Other interventions aimed at overcoming the immunological defects in CVID such as interleukin-2 therapy are being studied but there is as yet insufficient evidence to support their routine use. The treatment of complications such as suppurative lung disease uses principles broadly similar to those used for cystic fibrosis, whereas the granulomatous complications involving the lungs and other organ systems are in need of much more research to define optimum therapies.

1. Common Variable Immunodeficiency (CVID)

1.1 Epidemiology and Clinical Aspects

Common variable immunodeficiency (CVID) is the commonest significant antibody deficiency of adults.[1] It was estimated to have a prevalence of 1 in 50 000 in Sweden[2] and if this data is applied to the UK it is clear that many cases remain undiagnosed. The majority of patients develop symptoms either in childhood or late adolescence, and present most commonly with recurrent sinopulmonary infections.[3] *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* are the commonest pathogens, yet infections with other organisms are still more common than in the general population. Examples include gut infections with *Giardia lamblia*, enteroviral CNS disease and joint infections with *Mycoplasma* spp. In addition to the infectious manifestations, CVID is distinct from other immunodeficiency disorders in being associated with chronic unexplained inflammatory disease of the lungs, gut, liver, spleen and skin, often with granuloma formation.[4-7] As well as an increased susceptibility to infection, there is also an increased incidence of malignancy and autoimmune disease. The spectrum of clinical manifestations in CVID has been extensively reviewed elsewhere.[3]

1.2 Causes of the Underlying Immunodeficiency

The mechanism(s) of the immunodeficiency in CVID have not yet been fully established, although numerous proposals have been put forward.[1,8] Lack of appropriate investigative techniques, such as the ability to determine B cell numbers and cell protein expression hampered early research in this area, and CVID undoubtedly is a collective term for a variety of antibody deficiencies of differing aetiology. Males with X-linked agammaglobulinaemia but low numbers of B cells, females with μ-chain gene mutations[9] or surrogate light chain gene mutations,[10] patients with Good syndrome, X-linked lymphoproliferative disease (Duncan's disease) or defects in the genes involved in the Hyper IgM syndrome, are likely to have been misclassified as 'CVID' in earlier work. A diagnosis of CVID nowadays requires exclusion of an increasing list of genetically defined defects, most recently mutations in inducible costimulatory molecule (ICOS).[11] Various attempts have been made to subclassify CVID based on antibody production in culture systems[12] or clinical and laboratory features,[8] but these are not in routine clinical use. A more recent method, currently in development for subdividing CVID, which correlates well with the groups of Bryant et al.[12] and clinical categories is the Freiburg classification.[13] This uses flow cytometric analysis of CD19 gated B cells (excluding those CVID patients with low B cell numbers or granulomatous complications) to define CVID Group I with a severe deficiency of switched memory B cells. Group I is further subdivided into Ia with elevated immature B cells, which is associated with splenomegaly and autoimmune cytopenias, and Ib with normal numbers of immature B cells (figure 1). This system is likely to be applied more widely as it is much simpler to perform than previous systems but it needs validation across other patient cohorts.

One of the most encouraging findings for future work in CVID has been that the humoral immunodeficiency may be at least partially reversible as demonstrated in certain clinical situations where patients with CVID have become infected with hepatitis B or HIV.[14-18] A further report describes the spontaneous recovery of CVID after 20 years and this possibility needs to be remembered when analysing other therapeutic interventions.[19]

As the primary manifestation of CVID is hypogammaglobulinaemia, initial work focussed on B-cell function. Studies stimulating CVID B cells *in vitro* in the presence of a variety of cytokines resulted in secretion of all the main immunoglobulin classes in most patients[20] suggesting that the primary abnormality did not lie within the B-cell compartment alone. However, some B-cell defects have been described in CVID: B-cell differentiation studies showed a reduction in CD21 expression on B cells and absence of enhanced expression of activa-

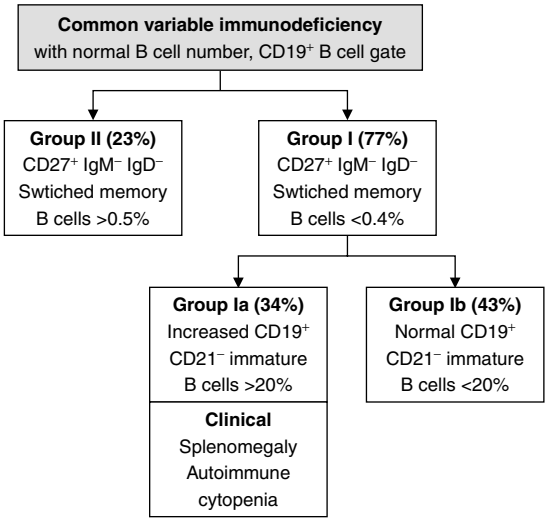

Fig. 1. Freiburg flow cytometric common variable immunodeficiency (CVID) classification. This shows the flow cytometric classification of CVID patients with normal B cell numbers. Patients with granulomatous complications have been excluded. The classification correlates well with the previous functional categories of Bryant et al.[12] Group I includes previous categories A and B and Group II contains category C. Early evidence also suggests that Groups II and Ib may retain limited vaccination responses, while Group Ia is associated with splenomegaly and autoimmune cytopenias. It is not clear if the splenomegaly is granulomatous in nature.

tion markers.[21] Defects in the protein kinase C (PKC) pathway have been demonstrated in CVID B cells in which PKC fails to activate and translocate to the plasma membrane following stimulation.[22]

Removing monocytes from mononuclear cell cultures in two patients with CVID led to increased proliferative responses to T-cell mitogens phytohaemagluttanin (PHA) and concanavalin (Con)-A.[23] Similar studies demonstrated impaired immunoglobulin production by CVID B cells *in vitro*, which was corrected by removal of monocytes from the culture system.[24] Monocytes from patients with CVID generate significantly greater quantities of reactive oxygen species following stimulation[25] and a greater proportion of monocytes from patients with CVID express interleukin (IL)-12 on activation than monocytes from normal controls.[26] It is likely that other inflammatory cytokines in addition to IL-12 are produced in excess by monocytes in CVID.

Numerous T-cell abnormalities have been identified in patients with CVID including defective T-cell activation following stimulation with anti-CD2,[27] super-antigens or anti-T-cell receptor (TCR) antibodies.[28] This suggests a defect in TCR-signalling, and impaired intracellular tyrosine kinase expression following TCR ligation[29] adds weight to this hypothesis. Abnormalities of cytokine expression in patients with CVID have been extensively reported, yet depend on the technique used to measure cytokines: for example, in culture supernatants or intracellular levels determined by flow cytometry. The variety of techniques and mitogens used as well as the likely heterogeneity of patients with CVID makes the literature on cytokines in CVID extremely confusing. The following is a synopsis.

A general reduction in IL-2 secretion into culture supernatants following mitogenic stimulation of cultured CVID T cells is well known.[30] Yet this is likely to reflect the reduction in CD4+ T cells and in particular CD45-RA positive cells in CVID, as intracellular production of IL-2 per T cell following mitogenic stimulation is normal in CVID.[31] IL-3 levels in CVID are variable[32] and IL-4 production is probably reduced in CVID, although studies are conflicting. IL-5 is normal or low, and certainly not elevated.[30,33] IL-6 can be elevated but probably reflects on-going infection.[34] IL-9 expression after stimulation is reduced[32] and IL-10 production is normal[35] yet is not successful at restoring immunoglobulin synthesis. IL-12 expression by lipopolysaccharide (LPS)-stimulated monocytes is increased in CVID compared with controls.[26] Serum tumour necrosis factor (TNF)α levels increase in CVID, particularly following infection or adverse reactions to intravenous immunoglobulin (IVIg) infusions, but production per lymphocyte is similar to controls.[31] The picture with interferon (IFN)γ is confusing, but there is a significant increase in the proportion of IFNγ-producing cells after activation in CVID compared with controls.[31]

Many abnormalities in T-cell subsets have been described in CVID.[36,37] Of particular significance, there is a reduction in CD4+ T helper cells, especial-

ly in patients with granulomatous manifestations, extremely low levels of naive CD45RA+ cells,[12,38] and an expansion of CD28− cells, particularly within the CD8+ T cell population.[39] T cells from patients with CVID, particularly the most severe form, have abnormalities of activation marker expression with elevated proportions of human leucocyte antigen (HLA)-DR+ cells, yet normal level of CD25 expression (despite elevated serum levels of soluble CD25).[40] In keeping with the fact that CVID is likely to represent a number of conditions resulting in hypogammaglobulinaemia there is no clear single defect and, although CD4+ T cells are perhaps the cell type in which the primary defect is most likely to reside, even this is not yet clear.

1.3 Genetics

Genetic explanations for the defects in CVID are only beginning to be established. Various groups have made associations between IgA deficiency and CVID and major histocompatibility complex (MHC) Class II/III. The +448 polymorphism of the TNFα gene has been associated with the granulomatous form of CVID.[41] A large microsatellite linkage study of 101 multiple case families with IgA deficiency and CVID demonstrated a strong susceptibility locus (IGAD1) lying in the telomeric part of the Class II region or the centromeric part of the MHC Class III region on chromosome 6.[42,43] Very recent evidence suggests a role for the inducible co-stimulatory molecule (ICOS), a member of the CD28/CTLA4 family. This is expressed on activated T cells and its ligand (B7H) is expressed on B cells and non-immune cells following inflammatory stimuli. ICOS has a role in T cell activation and proliferation as well as humoral immunity, it is critical for CD40-mediated antibody class switching[44] and may play a protective role in inflammation.[45]

Grimbacher et al.[11] demonstrated a defect in ICOS in a subset of patients with CVID. Four patients from two families out of 32 patients tested were found not to express ICOS on activated T cells. ICOS mRNA was truncated with loss of exons 2 and 3 due to a 443bp deletion resulting in loss of the extracellular and transmembrane domains. These patients all had low levels of B cells (which were able to synthesise IgA and IgG *in vitro*), high levels of B7H (ICOS ligand), recurrent pulmonary infections, one had a vulval carcinoma aged 34 years, and one had salmonellosis, however none had splenomegaly, granulomata or autoimmune disease. The discovery that ICOS mutations are responsible for the defect in a subset of patients with CVID points to problems in co-stimulation, which may lead to the discovery of further genes involved in CVID in this gene family and potential therapeutic targets.

2. Immunoglobulin Replacement Therapy

The mainstay of therapy in CVID remains replacement IVIg therapy, which has replaced intramuscular immunoglobulin as there are fewer adverse effects and a greater amount can be infused. A number of studies have established the efficacy of IVIg[46-49] and further studies have demonstrated reduced infection rates if the trough IgG level was maintained above 5 g/L;[50] in X-linked agammaglobulinaemia a trough of greater than 8 g/L resulted in a lower infection rate.[51] In a multicentre, randomised study comparing IVIg 300 mg/kg with 600 mg/kg every 4 weeks for adults with hypogammaglobulinaemia and 400 mg/kg with 800 mg/kg every 4 weeks in children with hypogammaglobulinaemia, a statistically significant reduction in infections was noted with no increase in adverse effects with the higher dosages.[52] The optimal trough level required to prevent infections in CVID has not been established, however, a dose of 200–400 mg/kg of IVIg given every 2–4 weeks would be what most centres use. It is important that the diagnosis is made early so that IVIg replacement therapy may be commenced before the onset of irreversible end organ damage.

IVIg requirement may vary as baseline IgG and rates of catabolism of IgG in patients vary widely;[53,54] dose and dose interval therefore need to be tailored to the individual patient. Patients with ongoing severe or recurrent infections, exudative enteropathy with increased IgG clearance, mycoplasma arthritis or low trough levels may require higher

doses of IVIg. A recent report describing progressive neurodegeneration in patients with primary immunodeficiency receiving IVIg highlights the importance for vigilance and the authors suggest that these patients may have had an unusual manifestation of their primary immunodeficiency, an autoimmune reaction against neuronal tissue, a yet unidentified pathogen or a complication of IVIg therapy.[55]

Subcutaneous immunoglobulin therapy (SCIg) has become increasingly popular particularly in children and patients with poor venous access.[56,57] SCIg is given more frequently than IVIg but in a randomised cross over study of 40 patients was found to be equally effective.[58]

Many centres provide training in IVIg home therapy and this has proved very popular as there are clear benefits for patients in increased flexibility, lifestyle and taking control of the management of their disease.[59-61] This training covers both intravenous and subcutaneous routes of administration of immunoglobulin.

The key property of IVIg at this dose is the large repertoire of antibody specificities it contains, which is the pooled product of many thousands of donations. Despite the large batch sizes currently used in immunoglobulin production, there remain surprising batch-to-batch variations in antibody titres to individual pathogens.[62] Further advances in CVID therapy with immunoglobulin will need to address these, and consideration of 'spiking' commercial products with high-titre antibodies to important pathogens. Further advances in IVIg or SCIg therapy will lie in improving formulations to reduce adverse effects associated with rapid administration, licensing of additional subcutaneous products, and consideration of the immunomodulatory effects of the excipients and stabilisers in commercial preparations. It has recently become feasible to nebulise immunoglobulin allowing direct delivery into the lungs and studies are planned to evaluate the potential of this route of administration.

In an attempt to improve and standardise the care and monitoring of patients with CVID receiving IVIg, discussions are taking place between the major centres treating immunodeficiency patients in the UK and guidelines have been produced. These are not intended to be rigid protocols but to offer practical guidance and evolve as information becomes available, and may be individually or locally modified. A summary of the guidelines for CVID is shown in table I.

3. Vaccination in CVID

The use of live vaccines in CVID is contraindicated in view of the possibility of prolonged excretion of a virus such as polio, which may then have the opportunity to revert back to virulence.[63,64] Even the use of killed vaccines is probably ineffective in view of the reduction in antibody, memory B cells[13,65] and T-cell responses.[66] It has been suggested that subsets of patients with CVID may retain some vaccination responses.[13] However, CVID is not characterised by excessive viral infections or conditions requiring a cell-mediated response such as tuberculosis, and some have argued that despite a poor antibody response, T-cell responses may be partially intact and, therefore, there may be merit in vaccinating to elicit the cell-mediated response. Progress in MHC Class I tetramer technology may allow these questions to be answered regarding the frequency of CD8 cytotoxic T-cell responses following, for example, influenza virus immunisation. Initial experience suggests that numbers of MHC Class I tetramer positive cells following vaccination with killed vaccines is low, although improvements in the sensitivity of the technology or vaccine design are likely.

4. Antibacterials

The other mainstay of therapy in CVID is antibacterials, which are used as treatment for breakthrough infections, as prophylaxis in patients with recurrent infections despite adequate doses of IVIg therapy and in suppurative lung disease. More attention should be given to this area in view of the lack of published evidence, and as there are good theoretical grounds for persisting/recurrent infection to modulate lymphocyte activation marker and CD28 expression, hence altering the ability of lymphocytes in CVID patients to migrate to relevant tissues

Table I. Monitoring guidelines in common variable immunodeficiency (CVID). The information in this table is intended for practical guidance, and local protocols and clinical indications may diverge from those described

Diagnosis	Hypogammaglobulinaemia with onset greater than 2y of age in the absence of known diseases or drugs causing antibody deficiency. Absent isohaemagglutinins and/or a poor response to vaccines (no live vaccines)
	Excluding XLPS, XLA, AID, X-HIM, leaky SCID and deficiency of μ-chain, λ5, Igα chain, BLNK
Baseline tests	FBC
	Liver function tests (ALP, ALT, calcium, bilirubin plus HBsAg and HCV PCR if indicated)
	Renal function tests including urinalysis
	Lung function tests
	Chest radiograph
	Circulating lymphocyte subsets (T, B and NK numbers)
	Serum immunoglobulins, serum and urine electrophoresis
	If IgG >3g/L perform IgG subclasses, tetanus, Hib and pneumococcal Ab titres and other vaccinations/infections as appropriate
	Anti-IgA antibodies (if IgA is low/absent)
	CT scan of lungs (if respiratory symptoms or signs present)
	Sputum culture (if productive cough)
	Store serum sample at −70°C
Treatment	IVIg or SCIg to maintain trough levels at 5–8 g/L
	Assessment for home therapy training programme
	Prompt treatment of infections and management of specific complications
Genetic counselling	Record pedigree
	Explain inheritance patterns of CVID and provide patient handout
	Identify any affected relatives and advise patient how to proceed
	Give patient details of the primary immunodeficiency association and the primary antibody deficiency booklet
Outpatient monitoring	Outpatient visit every 6–12 months (or depending on clinical situation)
	Monitor infection frequency, complications of treatment and disease, overall health
	Four monthly liver function tests, and trough IgG levels and CRP (home therapy team)
	FBC 6–12 monthly (haematinics iron, TIBC, ferritin, B12 and folate as required)
	Annual circulating lymphocyte phenotypes
	Lung function tests annually: spirometry, lung volumes and transfer factor (imaging as indicated clinically)
	Sputum culture (if productive cough)

Ab = antibody; **AID** = activation-induced cytidine deaminase; **ALP** = alkaline phosphatase; **ALT** = alanine amino-transaminase; **BLNK** = B-cell linker; **CRP** = C-reactive protein; **CT** = computed tomography; **FBC** = full blood count; **HBsAg** = hepatitis B surface antigen; **HCV** = hepatitis C virus; **Hib** = *Haemophilus influenzae* type b; **IVIg** = intravenous immunoglobulin; **NK** = natural killer cell; **PCR** = polymerase chain reaction; **SCID** = severe combined immunodeficiency; **SCIg** = subcutaneous immunoglobulin; **TIBC** = total iron binding capacity; **X-HIM** = X-linked hyper IgM syndrome; **XLA** = X-linked agammaglobulinaemia; **XLPS** = X-linked lymphoproliferative syndrome.

or to respond to normal signalling events. Optimum prophylactic antibacterial therapy in patients with CVID remains to be determined, although numerous regimens are used clinically on a purely empirical basis.

In a recent survey of 37 patients receiving IVIg, 101 infections were documented over a 1-year period, and of these 71 were respiratory and microbiological culture was obtained in only 30%.[67] The authors suggested that greater use of microbiological culture, treatment guidelines and closer liaison with general practitioners could improve the management of infective episodes. In patients with respiratory infections or suppurative lung disease, early involvement of physiotherapy is also of importance.

One antibacterial frequently used in CVID in the setting of recurrent infections on the background of

documented structural lung damage is the fluoroquinolone ciprofloxacin. Long-term fluoroquinolone prophylaxis may offer enhanced protection from chronic pulmonary *H. influenzae* infection; however, there is as yet no published data to support this approach. Ciprofloxacin is a bacterial DNA gyrase inhibitor, which in addition to its antibacterial effects has been found to have immunomodulatory properties.[68]

A difficult problem in CVID is infection with *Mycoplasma* spp., which can cause arthritis and meningitis as well as pulmonary infections. There has been some success in treating arthritis and meningitis with the pleuromutilin antibiotic, valnemulin (Econor®[1]),[69] when combinations of doxycycline and macrolides have failed to clear the infections. It is not clear how long this needs to be given and to what extent resistance will develop. The current approach is to establish the sensitivities and where possible to use combination therapy in an attempt to avoid the emergence of resistance.

5. Corticosteroids

Despite CVID being an immunodeficiency, there are occasions when immunosuppression with corticosteroids is required, for example to control CVID-associated granulomatous conditions and inflammatory bowel disease. This therapy carries the potential risk of precipitating overwhelming infection, and further studies of immunosuppressive agents are required to determine suitable alternatives to corticosteroids, and/or targeting corticosteroid therapy more accurately.

There has been anecdotal use of enteric-coated budesonide in a small number of patients with CVID inflammatory gut disease. The aim being that high first pass liver metabolism limits the systemic adverse effects, while treating the site of inflammation. Newer agents such as fluticasone may have even higher first pass metabolism, although no controlled studies exist to support their use in patients with CVID.

A subset of CVID patients have granuloma formation in the lungs, liver, spleen, skin and eyes, and some reports suggest a benefit from corticosteroids in these patients.[5-7,70] This area of the management of CVID remains difficult and studies into new approaches are needed.

Corticosteroids may also be used in the treatment of CVID associated immune thrombocytopenia (ITP); however, other modalities such as high-dose IVIg (hdIVIg),[71] anti-Rhesus D antibodies[72] or anti-B-cell therapy with rituximab may be considered. Rituximab an anti-CD20 monoclonal antibody is an attractive therapy as any subsequent lowering of immunoglobulin production is unlikely to be of concern in view of ongoing IVIg replacement; however, it has not been shown to be universally successful in chronic ITP.[73,74]

6. Surgery

Surgery to remove localised diseased lung in bronchiectasis has been shown to be of benefit in a study of hypogammaglobuliaemic patients followed up for between 3.5–5 years[75] in which all patients experienced considerable reduction of symptoms including cough, sputum production, antibacterial use and hospital admissions. This approach aims to remove a segment or lobe of bronchiectatic lung to prevent this acting as a focus for progression to other areas of the lung.

A subset of patients with CVID have undergone splenectomy to treat immune thrombocytopenia or granulomatous disease, and it is not clear whether this results in increased infectious episodes in the setting of adequate immunoglobulin replacement.

7. Immunomodulatory Interventions

7.1 Cytokines

T cells from patients with CVID have been shown to have numerous functional defects including a low production of IL-2, which was partially corrected with exogenous IL-2.[76] In a study of five patients given human recombinant IL-2 conjugated

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

to polyethylene glycol (PEG-IL-2), *in vitro* immunoglobulin production was enhanced, including anti-tetanus responses, but with no concomitant change in *in vivo* levels of immunoglobulins.[77] Further studies in which patients with CVID were treated with weekly subcutaneous injections of PEG-IL-2 showed enhanced T-cell proliferation, normal IL-2 production, boosted B-cell differentiation factor (BCDF) secretion and B cells responsive to differentiation signals after 12 weeks. During treatment, four of five patients produced detectable serum antibody to keyhole limpet haemocyanin (KLH).[78,79]

More recently 10 CVID patients with defective IL-2 synthesis *in vitro* were treated with natural human IL-2 in a placebo-controlled, double-blind, crossover study over a period of 12 months.[80] There were no significant adverse effects reported but *in vivo* IgG synthesis was not stimulated, although a few patients had an *in vitro* increase in IgG and/or IgM production following poke weed mitogen (PWM) stimulation in culture. However, there was a significant reduction in infections 6 months after (but not during) the study.

These data suggest some potential benefit from this form of therapy, but further work with longer, larger studies and more clinical endpoints is needed if this type of therapy is to become routine. The effect on *in vivo* vaccination responses to a panel of antigens in terms of both antibody and cytotoxic T-cell analysis using tetramers while on PEG/IL-2 therapy would also be of considerable interest. In addition, any expansion of the depleted CD27+ IgM−IgD-switched memory B-cell compartment should also be determined.

IL-10 plus anti-CD40 *in vitro* can enhance IgG and IgA production by B cells from patients with CVID.[20,81] This effect has not been established *in vivo* and it remains to be seen if IL-10 is sufficiently well tolerated to attempt this in therapeutic trials in patients with CVID. Therapeutic intervention with IL-10 in patients with Crohn's disease is currently an active research area,[82] which may have important implications for the treatment of patients with CVID.

7.2 Vitamin A and Analogues

Retinoids are vitamin A derivatives that have profound effects on cellular development, enhance proliferative responses to mitogens and increase immunoglobulin production by B cells.[83,84] Retinoic acid was shown to enhance IgM synthesis by hybridomas constructed from B cells from patients with CVID but not from hybridomas produced from controls or patients with IgA deficiency.[85] Additional studies confirmed that IgM synthesis, but not that of the other immunoglobulin isotypes, could be enhanced by retinoic acid stimulation of CVID hybridomas.[86] The vitamin A analogue 9-*cis* retinal augmented IgM, but not IgG synthesis, from both normal and CVID B cells in culture, although synthesis from patients with CVID was significantly lower than that of controls. Other analogues (13-*cis* retinoic acid and all-*trans* retinoic acid) had no effect.[87]

A study of 16 patients with CVID did not demonstrate any deficiencies of retinol, tocopherol or antioxidant capacity (measured as TEAC, Trolox-equivalent antioxidant capacity). However, there were significantly reduced plasma ubiquinol levels, an important endogenous reactive oxygen scavenger.[88] Serum vitamin A levels were found to be decreased in CVID[89] and vitamin A supplementation (6500 IU/day in an open-label study of six vitamin A-deficient patients with CVID for 6 months) demonstrated an increase in serum IgA and IL-10 levels, and a significant fall in serum TNFα and neopterin levels. No change was seen in serum IgM levels, yet IgG production from stimulated B cells (since the patients were undergoing IVIg therapy during the trial) increased to normal in 3 of 6 patients.[89] It may be that the vitamin A deficiency in these patients was secondary to chronic infection, and larger trials with clinical outcome measures of vitamin A therapy in vitamin A deficient CVID patients would be required to confirm these findings.

7.3 Cimetidine and Ketoprofen

The histamine receptor type-2 (H_2) antagonist cimetidine has been shown to have mild immuno-

modulatory properties,[90] mainly enhancing cell mediated immunity by increasing proliferative responses to mitogens and antigens[91] and inhibiting T-cell suppression.[92] Early studies with cimetidine therapy for CVID showed a decrease in T-suppressor cell activity in three patients and increases in endogenous antibody production in one patient.[93] Treatment of a patient with familial CVID using cimetidine (1200mg daily in three divided doses for 6 months) resulted in no change in serum immunoglobulin levels (the patient did not receive IVIg therapy with the cimetidine therapy). There were transient increases in lymphocyte proliferation to mitogens, which were not sustained during the trial.[94] The patient reported a reduction in respiratory infections, but with only one patient in the study a demonstrable therapeutic effect of H_2-receptor antagonists in CVID remains to be proven.

A further study suggested improved *in vitro* antigen-specific antibody synthesis in two patients with CVID taking the oral cyclooxygenase and lipoxygenase inhibitor ketoprofen. Addition of ketoprofen *in vitro* to B cells from four other patients with CVID resulted in improved proliferation and differentiation.[95] There have been no other studies confirming these interesting findings.

8. Lessons from HIV Infected CVID Patients

There are now a number of reported cases of CVID where patients have acquired HIV subsequent to the diagnosis of hypogammaglobulinaemia.[15-18] A striking feature of these patients is that following HIV infection, antibody production of the IgG and IgM class but not IgA is restored, to the extent that IVIg replacement therapy could be stopped. Hypergammaglobulinaemia is a common finding of HIV infection itself,[96] however, usually IgG_1 and IgG_3 subclasses are elevated, often with a concomitant IgG_2 and IgG_4 deficiency. Indeed, patients with AIDS may have profound IgG_2 subclass deficiency including specific antibody deficiency despite a high total IgG;[97] such patients are susceptible to a range of pyogenic infections and may require IVIg replacement therapy.

Early studies by Lane et al.[98] demonstrated that HIV infection causes dysregulation of both T-cell-dependent and -independent B-cell responses to mitogen-induced lymphoproliferation, while B cells spontaneously secreting immunoglobulin are increased. It has been suggested that HIV antigens may drive the hypergammaglobulinaemia. Previous studies of antigen responses in CVID have examined T-cell responses to HIV *env* peptides. Whereas normal T cells proliferate to this stimulus, those from CVID patients do not.[66] However, there are many more candidate antigenic determinants of HIV that could have a lymphoproliferative effect.

In patients with monoclonal gammopathy and HIV infection a fall in paraprotein level has been seen to accompany the fall in viral load following the initiation of antiretroviral therapy.[99] However, in the CVID patient with HIV infection described by Jolles et al.[15] antibody production was maintained despite the initiation of antiretroviral therapy, implying that either productive infection may not be necessary to achieve the observed restoration of B-cell function or that low levels of HIV replication, perhaps within lymph nodes, is sufficient. Another interesting finding was the restoration of low levels of specific antibody responses (e.g. tetanus toxoid) without booster vaccination. The spontaneous recovery of such T-cell dependent antibodies suggests the possibility that in CVID memory T cells may exist but are suppressed.

In the CVID patient described by Wright et al.[18] both B- and T-cell responses were abnormal *in vitro* following HIV infection. There was failure of PWM stimulation and patient lymphocytes could not be stimulated to produce antibody with normal T cells or support antibody production in normal B cells. While *in vitro* assays were abnormal, *in vivo* antigen responses were normal. Webster et al.[17] had similar *in vitro* results, however, they were also able to demonstrate a high level of spontaneous immunoglobulin production, which may correlate with the *in vivo* polyclonal hypergammaglobulinaemia observed.

B-cell proliferation has been induced in patients with CVID using an antisense oligomer to the *rev*

gene of HIV-1.[100] This mechanism is T-cell independent, since the addition of T cells to the antisense oligomer treated B cells had no effect on proliferation. It is suspected that upregulation of the transcription factor (nuclear factor) NF-κβ is the mechanism by which the anti-*rev* oligomer achieves the observed effect on antibody production. Whether this effect could further be exploited to facilitate T-cell dependent B-cell proliferation requires further exploration, perhaps also utilising HIV envelope peptides to activate T cells. It would be possible to assess the effects of different peptides from HIV on CVID B cells, T cells and monocytes using DNA microarrays to dissect out their downstream effects in defined cell populations.

9. Modulation of Fc (constant fragment) Receptors

It is possible that in the future strategies which augment MHC class I-related neonatal Fc receptor (FcRn) function or expression may be used as this receptor recycles IgG bound to FcRn back to the cell surface maintaining the half-life, while unbound IgG is broken down. This may prolong the half-life of IVIg.[101]

Given the elevated monocyte IL-12 expression in patients with CVID, and the potential this has for enhancing IFNγ expression and hence granuloma formation, attempts to modulate this would be a useful therapeutic strategy. IL-12 expression is affected by the degree of cross-linking of Fcγ receptor type I.[102] In experimental settings, dopamine agonists (bromocriptine, leuprolide and pergolide) have been shown to up-regulate Fc receptor (FcR) expression, particularly those operating through dopamine D_2 receptors.[103] An obvious study would be to attempt to up-regulate FcR expression in patients with CVID by means of dopamine agonist drugs, with the hope that the enhanced FcR expression in the presence of high concentrations of exogenous IgG would result in IL-12 down-regulation and, thereby, in reduced granuloma formation.

10. Conclusions

CVID continues to pose a number of scientific and clinical challenges, not least reducing the number of undiagnosed patients. The genetic defects are only beginning to be discovered and there are numerous clinical areas, such as the granulomatous complications, inflammatory gut disease and respiratory disease, which pose difficult management problems. There is little evidence to support the current routine use of cytokines such as IL-2; however, some of the results are encouraging and there may be valuable lessons to be learned from patients with CVID infected with HIV and hepatitis B in whom antibody production has been partially restored. It is likely that improved disease classification and advances in technologies such as MHC Class I tetramers, DNA microarrays, and our understanding of signalling in particular costimulatory pathways for B cells and T cells will shed light on novel defects in CVID and how treatment may be improved. The new data regarding ICOS defects in a subset of CVID patients may point towards ways of bypassing this and other defects of this type. Currently, however, the mainstays of treatment remain immunoglobulin replacement, early appropriate antibacterial therapy and the careful management of complications.

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