SECTION 5

Monitoring immunoglobulin replacement therapy

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Initiation of immunoglobulin replacement therapy

Ideally immunoglobulin replacement therapy (IRT) should be managed - or at least initiated - in regional specialist primary immune deficiency (PID**)** centres to enable equitable geographical access to medical and nursing expertise in these diseases. However, as IRT therapy has become the standard of care in patients with PIDs and secondary immune deficiencies (SIDs), and with the documented benefits of IRT, an increasing number of patients on IRT are reliant on a diversity of medical specialists.

Formal links should exist between regional immunology centres, with recognised referral treatment pathways. Services offered at national centres in different countries vary depending on geography, available resources, and expertise, but all should aim to reach internationally agreed standards of care, as in other rare diseases. Registries are an essential part of patient care.

The reality in South Africa is that patients with PID or ‘inborn errors of immunity’ are treated by their primary care physician (PCP) due to a lack of resources. Successful patient outcomes depend on an efficient ‘care team’ based on a coordinated multidisciplinary approach. Effective communication between team members is key.

Patients with PID experience the same medical issues and challenges as their counterparts without PID. In South Africa, the PCP manages the majority of the patient’s general medical needs and serves as a nexus for patient care.

Patient support organisations and groups such as the Primary Immunodeficiency Network of South Africa and the International Patient Organisation for Primary Immunodeficiencies, are invaluable in assisting healthcare practitioners with access to information for best care practices. They also play a key role in patient empowerment. From the start, patients’ expectations must be defined. They must be made aware of the benefits of IRT but unrealistic expectations should also be discussed in order to ensure continued follow up.

The patient should be encouraged to keep his/her own electronic or hard copy records (Ig passport) of the product brand, method of administration, the product number, dates of infusion with notes on any side effects experienced, infections, and need for antibiotics in interim periods or hospitalisations, as well as the Ig trough level prior to first and subsequent infusions.

This will assist the physician and the patient to monitor efficacy, and objectively document the benefit and need, or not, for continuation of the product or switching to another brand of Ig if and when available. Most patients will tolerate the first product choice but 10%-15% of patients will experience some side effects and may need to switch to another product or prophylactic treatment of side effects.

Serum samples must be saved of the patient at initiation of first infusion – for retrospective review of viral infection acquisition. Infection screening must rely on polymerase chain reaction not antibody measurement in antibody deficiency states, and IRT.

Monitoring of patients on IRT administration

Clinical review of all patients on IRT should be ensured for best outcomes. In general, the routine review should take place at three- to six-monthly intervals. In the case of intercurrent illness or other change in clinical status, the patient should also be reviewed at the time of the illness. It is important that patient evaluation is conducted by a clinical specialist or immunologist with training and experience in immunodeficiencies.

A coordinated multidisciplinary approach to care for patients should ideally include a specialist trained in the caring of these patients. An immunologist or pathologist can assist with the accurate assessment of laboratory tests, a pulmonologist/allergologist can manage concurrent lung disease and allergies, and a rheumatologist with any rheumatological diseases, which often co-exist in PID and SID patients.

In addition, there should be a coordinated approach to care involving a general practitioner/physician/pediatrician and physiotherapist (for patients with lung disease) to whom the patient can present to with routine issues between specialist review appointments.

At each review, all patients are routinely monitored to determine current clinical status which includes as minimum:

1. A good history.
2. Physical examination.
3. Blood counts.
4. Chemistry screening.
5. IgG trough levels at six- and 12-monthly intervals in uncomplicated patients, but more frequently in patients with breakthrough infections or disease complications.

Additional review monitoring of patients with lung disease includes:

1. Spirometry.
2. Chest x-ray (CXR).
3. High-resolution computed tomography (HRCT) scan of the chest **
4. Carbon monoxide diffusion capacity if available.

** The general consensus is that HRCT of the chest to monitor for bronchiectasis should not be performed as a routine but should be dictated by clinical status and if indicated, at the start of IRT. These patients also need routine review with every visit for the development of new morbidities, specifically progressive lung disease, which may be subclinical.

Table 1: Measurement parameters of patients on IRT

Test	Interval	Potential complication
Full blood count	3-6 monthly	• Anemia • Cytopenias
Creatinine	3-6 monthly	Renal failure (a rare complication of IVIg)
Liver function	3-6 monthly	Abnormal liver function tests can detect the possibility of blood borne viral infection where early diagnosis and treatment is beneficial
Trough IgG after established IRT	3-6 monthly	Level 5g/L associated with prevention of acute bacterial infection. 7-9g/L further reduction in infections. It is extremely important to keep in mind that trough IgG levels are not a valid method of monitoring IRT in patients with selective antibody deficiency and IgG subclass deficiency
Weight/height	At each visit for children and 6 monthly for adults	To adjust the dose as indicated and to monitor growth and general well being
Blood pressure	At each visit	Routinely during Ig infusions
Spirometry	Yearly or as indicated by clinical status	
Chest x-ray	As indicated by respiratory status	

Table 2: Other tests that may be considered when monitoring patients on IRT

Test	Interval	Complication
High-resolution computed tomography (chest)	Baseline in adults then as indicated by respiratory status/4 yearly	• Bronchiectasis granuloma • Lymphoid interstitial pneumonia
Ferritin	6 monthly	For early detection of iron deficiency
LDH		
C-reactive protein	3 monthly	Has been advocated however the clinical significance of an elevated result remains uncertain. Might be elevated in bronchiectasis/lymphoid interstitial pneumonia

Assessment using the common variable immunodeficiency disorders (CVID) severity score (CDSS) is recommended for patients with CVID and CVID-like disorders. The CDSS focuses primarily on cumulative organ damage as a result of infections, autoimmunity, or inflammation. The severity of the complications has been arbitrarily divided into three categories:

1. Mild: manifestations can be easily treated and do not cause long-term morbidity.
2. Moderate: conditions do cause short and long-term morbidity and may not be reversible.
3. Severe: conditions are either life threatening or have the potential to cause severe disability such as visual loss or severe pulmonary dysfunction.

The CDSS can be useful in busy clinics or where the patient is reviewed by different clinicians on separate visits. It may alert a new physician to the likely severity of the CVID/CVID-like disorder in an individual patient and help achieve consistency in how often patients are followed up.
(CDDS can be viewed at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6172311/)

Other special considerations in chronic monitoring:

1. ***Transitioning of adolescent patients:*** transition from adolescence to adulthood is characterised by changes of many kinds: physical, social, psychological, educational, and domestic and the chronic disease itself. The healthcare provider that will be responsible for the care of the transitioning adolescent patient, must be identified and introduced timely, and an individualised transitioning plan has to be designed. The adolescent needs to be coached and empowered to become independent (e.g., parental management should be limited), and a patient support/buddy system should be in place. A social worker or psychologist may need to be involved. Paediatric patients are at great risk for comorbidities and psychological instability at this crucial point if not supported effectively and empowered.
2. ***Pregnancy:*** an obstetrician must be involved in the PID care team and Ig requirements must be monitored more frequently.
3. ***Growing children:*** may have rapidly increasing requirements of IRT.
4. ***Weight loss:*** May result in decreasing requirements of IRT.

An annual patient annual risk assessment (e.g., King's College Hospital) is recommended for those who require more rapid and frequent Ig are needed (febrile patients or those with gastrointestinal or lung disease). (Annexure A).

Annexure A: Example of an annual patient annual risk assessment

Name: _____

Date of birth: _____

Hospital number: _____

Assessed by: _____

Diagnosis: _____

Current evidence for diagnosis in this patient: _____
_____
_____

Current treatment: _____

Potential benefits treatment:
_____
_____
____

Potential risks of treatment: _____

_____
_____

What type of evidence supports the use of the treatment? _____
_____
_____

What peer review has been used to assess the treatment?
_____
_____
_____

Are changes to diagnosis or treatment indicated? _____
_____
_____

Have yearly investigations been done? (e.g., serum save, hepatitis serology, lymphocyte subsets, lung function test)
_____
_____
____

The risk assessment had been discussed with the patient: Yes /No

Signed: _____
__

Date: _____

If clinical efficacy of IRT declines and steady state serum Ig measurements decay, consider the following:

- Emerging new comorbidities.
- Persistent low grade/acute infection.
- IgG loss – gut/kidney.
- Poor adherence.

Establishing ideal IgG trough levels

Numerous studies have shown less frequent bacterial infection and improved outcome in PID with higher doses of IVIg IRT. [1-8] In a double-blind, multi-centre cross-over trial, 50 children were randomised to receive either 0.4g/kg or 0.8g/kg of intravenous Ig (IVIg) every four weeks (adults in the study received 0.3g/kg or 0.6g/kg).

The number of immunodeficiency-related infections was reduced in the high dose IVIg group ($P<0.004$), demonstrating a definitive benefit of higher doses. The IgG trough level in the low-dose group was 6.4g/L compared with 9.40g/L in the high-dose group, suggesting an importance of maintaining a higher trough level.[1]

When IVIg is administered, there is a rapid increase in the serum IgG (sIg) concentration, designated the peak IgG level, which gradually decreases over time before the next infusion. This is the trough IgG level and has been viewed as an important guide to evaluate the adequacy of a

particular IVIg dose. Sufficient trough levels needed for optimal protection against bacterial infections in patients with PID are yet to be established. [1-5]

Pneumonia is a frequent complication in patients with PID and can be severe, frequently requiring IV antibiotics and hospitalisation.[9] By preventing pneumonia, IVIg therapy can also reduce its complications, including bronchiectasis and progressive lung disease.

In order to determine the optimal IgG trough level, numerous studies have focused solely on the efficacy of IVIg in preventing pneumonia. A meta-analysis done by Orange *et al*[2] demonstrated significant progressive decreases in pneumonia incidence associated with an increase in trough IgG.

The studies evaluated in the meta-analysis excluded intramuscular and subcutaneous (SC) administration routes, because these routes of dosing result in different pharmaco- kinetics without comparable trough levels. Pneumonia incidence rates were compared for IgG trough levels of 5, 6, 7, 8, 9 and 10g/L and IVIg doses of 0.1, 0.2, 0.3, 0.4), 0.5 and 0.6g/kg.[2]

The types of PID included in the studies were CVID, x-linked agammaglobulinemia (XLA), agammaglobulinemia, hyper-IgM, IgG subclass deficiency, specific antibody deficiency, ataxia telangiectasia with hypogammaglobulinaemia and hyper-IgE syndrome. The median treatment interval between IVIg infusions amongst the studies was 24.6 days.[2]

Across all the included studies, a linear increase in the trough IgG level was noted with increments in IVIg dose administered. The trough IgG increased with 1.21g/L with each additional 0.1g/kg in IVIg dose.[2] Bear in mind that patients with enteropathy, granulomatous disease, protein losing conditions will not reach an adequate increase in IgG trough when increasing the Ig dose.[6]

The pneumonia incidence demonstrated a statistically significant reduction of 27% for 1g/L increase in trough IgG. Maintenance IgG trough levels of 5g/L was associated with a five-fold increase in pneumonia incidence as opposed to a trough level of 10g/L. Dose increments up to at least 0.6g/kg were also associated with diminished pneumonia incidence. [2,7]

Bronchiectasis is a feared complication of pneumonia, a major cause of progressive chronic lung disease in PID patients.[10] In a study of serial lung function tests among PIDD patients, changes in forced expiratory volume in 1 second (FEV_1) increased linearly with IgG trough level over the evaluated range of 8–11g/L.[11] In a survey of 90 patients with enteroviral infection, a link between low levels of IgG and infection was found, with higher trough IgG levels contributing to a reduced incidence.[7, 12]

In primary antibody deficiencies, where the defect is the inability to produce an effective antibody response to pathogens, only IgG antibodies might be replaced by IV or SC administration. Clinical phenotypes of CVIDs and XLA are quite variable, even within one disease or syndrome. Therefore, the suggested protective trough IgG level of 10g/L might not be considered a general goal and only large prospective multi-centre studies might help to identify subgroups of patients at high infection risk.

A prospective study done by Quinti *et al*[6] identified prognostic markers and risk factors for associated clinical co-morbidities in a large cohort of patients with primary antibody deficiencies over a long cumulative follow-up period. This was a ‘real-life’ observation of patients treated with lower doses of IRT, a common practice in many immunological centres.

After starting IRT, a reduction in the incidence of severe acute infections was observed. Thereafter, this incidence remained low and constant over time. The trough IgG levels measured at the time of each episode of pneumonia were extremely variable and were not lower in those patients who experienced one or more episodes of pneumonia. It was noted that in order to prevent bronchiectasis, our efforts should be directed at the prevention of pneumonia.

In CVID patients, the major risks for bronchiectasis were the age of disease onset and low IgA levels.

This data allowed the identification of a clinical phenotype characterised by a high pneumonia risk: patients who had low IgG and IgA levels (<0.07g/L) at diagnosis and patients who have bronchiectasis.

The hazard risk for pneumonia is increased in those patients who did not reach an IgG trough level>4g/L. This data does not indicate that the protective trough IgG level is 4g/L, but it demonstrates a higher risk to develop pneumonia at low IgG levels. It is therefore suggested that the controversial recommendation to start Ig replacement treatment when IgG levels are <4g/L should be supported, even before the development of a severe infection.[6]

Low IgG and IgA at diagnosis and very-low IgA levels, reflecting a severe impaired isotype switching process, were major independent risk factors for lung complications, confirming that loss of function of memory B cells represents a major cause of CVID-infectious-associated clinical conditions, as demonstrated in CVIDs with bronchiectasis. [6,13,14,15]

While infections are the main cause of morbidity in all XLA patients, non-infectious complications (autoimmunity, lymphocytic hyperplasia, and enteropathy) are unique clinical phenotypes in subgroup of CVIDs patients who may not develop infections and may have an unclear benefit from Ig replacement.[16] The effect of therapy with Igs at replacement dosage for noninfectious co-morbidities (autoimmunity, lymphocytic hyperplasia, and enteropathy) remains to be established.[6]

Individualised treatment

A common clinical approach is to individualise treatment, identifying the ideal biological level for a given patient that will prevent breakthrough infections. [8,17-19] There is consequently some confusion over defining optimal dosages and target trough IgG levels for patients.

Earlier evidence regarded 5g/L as the appropriate minimum trough level, but this was subsequently increased to higher target levels. Recommendations were made to ideally reach levels approaching or exceeding the lower limit of IgG concentration for normal healthy adults. Most published guidelines recommend trough IgG levels of around 6-8g/L to be achieved with a dose of 04g/kg every three to four weeks, but the consensus is based largely on expert opinion and systematic reviews of limited data. [20,21,22] Other guidelines recommended target trough levels of 6.5-10g/L.[2,7,16,23-26] These recommendations therefore infer that different requirements for IgG exist between and within a given PID group.

Dosages should approach IgG trough levels as recommended by guidelines but should be adjusted upwards as needed to minimise infection in a specific patient. The optimal IgG level that prevents bronchiectasis/infection is not uniform in all patients.[17]

A prospective observational cohort study, published by Lucas *et al* [17] determined the relationships between doses of replacement therapy, infection rates, and trough IgG levels and compared these for patients with different clinical CVID phenotypes and common complications. Furthermore, this data was generated from a substantial group of patients with CVID followed up over 22 years in one centre using validated data (741 patient-years). The policy of adjusting the dose of replacement therapy to reduce the infection rate to a minimum in a given patient has generated a wide range of dosage regimens for analysis. This study provided evidence to support the clinical view that the trough IgG level and dosage of IRT to maintain a minimal infectious burden is unique to each individual.[17]

Patients with a CVID had a range of trough IgG levels that prevented breakthrough bacterial infections ranging from 5-17g/l, viral and fungal infections were rare. Doses of replacement Ig to prevent breakthrough infections ranged from 0.2-1.2g/kg/mo. [17]

Patients with bronchiectasis required twice as much replacement therapy to achieve the same IgG level compared to those patients free of bronchiectasis. Whether this is a result of increased catabolism or loss remains unclear. The increased doses of IRT were sufficient to prevent an excess of infections, regardless of previous structural damage. Those with proven bronchiectasis or particular clinical phenotypes required higher replacement doses.[17]

Five distinct clinical phenotypes were proposed for CVID:[27]

1. No complications.
2. Autoimmunity.
3. Polyclonal lymphoproliferation.
4. Enteropathy.
5. Lymphoid malignancy.

Patients without disease-related complications received significantly lower doses of IRT (compared with patients with other phenotypes) and had significantly lower infection scores. Those with lymphocytic interstitial pneumonia, cytopenia, and enteropathy received higher doses of IRT. Patients with XLA needed a slightly higher range of IgG levels to stay infection-free (8-13g/L).[17]

In many guidelines and centres, patients without chronic lung disease are started on 0.4g/kg/m and patients with bronchiectasis on 0.6g/kg/m.[19-21] When breakthrough infections occur, doses are adjusted accordingly. Three moderate infections per year justify an increase in dose of around 0.15g/kg/m.

The IgG trough level should therefore be individualised for each patient. The goal is to keep patients' infection free, rather than to achieve a particular IgG trough level. This level will be different for each patient and will be influenced by the different clinical phenotypes. [8,17]

Biological IgG level

The term 'biologic IgG level' was described to represent the minimal serum IgG levels that renders a patient as disease free as possible. It is recommended that physicians' plot their patients' IgG levels over time against documented infections to identify the biologic IgG level and to aim to keep the IgG level at or just above that biologic IgG level. This will optimise care and address IgG reimbursement queries.[17]

Patients should therefore be treated according to their clinical condition than to achieve any prior designated IgG trough level.[8] Nevertheless, monitoring serum IgG levels at routine intervals is important for several reasons. They may serve as markers for adequacy of therapy and enable comparison of one regimen with another. Thus, in patients who experience exacerbations of underlying infection and/or chronic nonspecific symptoms when the IgG trough level falls below a certain value during treatment with intermittent IVIg infusions, that value may serve a target for SC therapy.

Monitoring the serum IgG levels also helps assess whether a patient may be experiencing increased gastrointestinal or renal protein loss and may require a higher dose or shorter dosing interval to maintain protection against infections.

In patients who do not have severe hypogammaglobulinaemia per se and/or who actually have elevated serum IgG levels because of monoclonal gammopathy or nonspecific polyclonal B-cell activation, monitoring the trough levels of specific antibody levels (e.g., against pneumococcal polysaccharides) may be preferable to using the total IgG level for monitoring the adequacy of therapy.[18]

Monitoring their IgG trough levels will do them more of a disservice and is not advised.[28]

Trough IgG levels should be monitored monthly after initiation of IRT.[16] A steady state should be reached after the sixth infusion. The dosage and administration interval should then be adjusted to achieve optimal clinical results, particularly when infections are not well controlled.

Once controlled, six to 12 monthly levels should be sufficient or whenever there is a significant infection and when the clinical response to treatment does not meet expectations. Treating clinicians should be mindful of changing weight (in children and pregnant women) and possibility of underlying protein-losing conditions, and doses should be adjusted accordingly. [8,28]

Periodic trough levels may detect non-adherence by patients who are receiving infusions at home (or self-administering SCIg at home). The IgG trough increase over baseline IgG level has been shown to significantly correlate with pneumonia susceptibility, with increases of <4.3g/L being inferior.[8] Patients with initial extremely low IgG levels, might benefit with initial higher dosages of IRT and some centres use an initial dose of 1g/kg administered slowly. [8,28]

It takes five to 12 weeks to achieve a steady state when initiating SCIg for the first time, or when making a change in the weekly dosage, or when switching from IVIg to SCIg. The (optimal IgG level) with SCIg replacement is the steady state level that can be drawn at any time and represents the level where the patient is infection free. The steady state IgG level is generally higher than the IgG trough levels observed at the end of the IVIg dosing cycle. Mean steady state levels of IgG ranges from 9.5-11.2g/L. [29,30,31]

Adjuncts to effective IRT/other measures of successful IRT

Ig replacement only partially replaces the antibody defect of primary antibody deficiency diseases. The more commonly available local Ig intravenous form, available by fractionation of South African plasma donations replaces antibodies specific to the antigen exposure of the donor pool.

While the South African donor pool numbers may be restricted compared to those of international plasma products, it may have the advantage of providing antibodies to locally relevant pathogens.

Several medical treatments are available for primary antibody deficiency PID to optimise health, improve quality of life and allow for normal growth and development in childhood and adolescence and participation as productive members of society later in life. These individual therapies have risk/benefit ratios which should be explained by the healthcare provider.

Antibiotic therapy is the mainstay of treatment for acute bacterial infections in primary antibody deficiency states. Their use is determined by the pattern of infection, the patient's specific immune deficit and whether the infection was acquired in the hospital or in the community.

Prophylactic antibiotic therapy is prescribed by some healthcare providers to provide additional protection in cases of breakthrough infections or with established end organ damage and ongoing foci of infection such as bronchiectasis.

This is given at low doses, usually about half therapeutic doses. The commonly used ones are amoxicillin, *bactrim* and azithromycin. Penicillin and or erythromycin may be used in the prophylaxis of meningococcal infection in patients with complement deficiency. There is currently no evidence for the emergence of drug resistance following the use of antibiotic prophylaxis. Antifungal prophylaxis is added to *bactrim* prophylaxis in primary neutrophil disorders such as chronic granulomatous disease.

Broad antibacterial and antifungal prophylaxis is given together with IRT in patients who are being investigated for combined severe immune deficit.

Vaccines may not work as well in the weeks to months after IRT is given because Ig may block the immune system from responding appropriately to the vaccine. However, vaccines do add additional protection. Correct indications and precautions with use of live viral vaccines should be discussed with a specialist.

Novel vaccines such as severe acute respiratory syndrome coronavirus 2 may play an important role in protecting PID patients while pooled antibody concentrations are still non-existent/low in donor plasma.

Recommendations

1. IgG level measurement:
    a. Measure IgG trough at the end of three- to four-week infusion cycles with IVIg IRT.
    b. Measure IgG steady state level at any time with SCIg IRT.
2. Trough IgG levels of 6.5-8g/L should be aimed for with IVIg IRT, but the dosage should be adjusted based on the clinical condition of each patient. Higher IgG trough levels of 8-10g/L may be required in selected patients.
3. The steady state IgG level with SCIg is generally higher than the IgG trough levels observed at the end of the IVIg dosing cycle, ranging from 9.5-11.2 g/L.

4. Each patient will have an optimal individualised IgG trough or steady state level that maximally prevents infections and dosages for IVIg and SCIg IRT should be adjusted accordingly.

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