National Cancer Control Programme

NCCP Guidance Document

Patient selection for the use of immunoglobulin replacement therapy in cancer patients with secondary immunodeficiency

Version	Date	Amendment	Approved By
1	14/01/2021		IAAI, IHS, NCCP, CCO CAG
2	01/12/2023	Update of Patient selection criteria to include post CAR-T therapy	NCCP Haemato-Oncology Clinical Leads Group

All comments and feedback are welcome at oncologydrugs@cancercontrol.ie

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1 Introduction

Immunodeficiency disorders involve malfunction of the immune system. Antibody deficiencies, a subset of immunodeficiencies may arise as primary or secondary disorders. Primary antibody deficiencies may arise from a known genetic mutation or be of unknown cause while secondary antibody deficiency disorders arise secondary to known causes such as a variety of malignant diseases (e.g. Chronic Lymphocytic Leukaemia (CLL), multiple myeloma (MM), post allogeneic Bone Marrow Transplant (BMT), lymphoma), CAR-T therapy, chronic infections, drugs, protein-losing states, systemic inflammatory diseases, trauma and iatrogenic factors. The focus of this guidance document is on the treatment of secondary antibody deficiency associated with haematological malignant disease. Several aspects of immunoglobulin (IgG) replacement following BMT are highly specialised and are outside scope of this document.

Antibody deficiencies clinically present as recurrent or persistent infection, but these disorders are also associated with a heterogeneous variety of other infectious and non-infectious complications and with a high incidence of chronic, structural tissue damage, particularly in the respiratory tract.

As with primary immunodeficiency the mainstay of treatment is replacement therapy with IgG with the aim of preventing infection. Variation in current clinical practice between specialities and the lack of high quality evidential base for the use of IgG replacement in secondary antibody deficiency has been acknowledged (1). Despite this there is broad agreement amongst UK and Irish immunologists on how such patients are assessed and managed (2). It is recommended that all patients with lymphoid malignancy or plasma cell dyscrasias should have their IgG levels measured prior to their first systemic anti-cancer therapy (SACT) treatment and prior to any major change in SACT treatment (3).

IgG may be administered intravenously or subcutaneously. Subcutaneous administration may offer a convenient alternative to intravenous therapy for some patients. Subcutaneous administration may involve more frequent infusions (weekly or biweekly) although the facilitated subcutaneous infusion of IgG replacement therapy offers a three

weekly subcutaneous treatment. The advantages of using this method of administration include fewer systemic adverse effects, more consistent serum levels of IgG and no requirement for venous access for infusion (4). The relative merits of intravenous and subcutaneous administration and hospital versus home therapy have been described in detail in the Primary Antibody Deficiency Model of Care (National Clinical Programme for Pathology)(5). These same issues apply in terms of administration of IgG replacement therapy for the treatment of secondary immunodeficiency in Ireland[1].

IgG is a pharmaceutical product derived from pooled human plasma. It acts by providing adequate concentrations of antibodies against a broad range of pathogens by providing passive immunity. This guidance will focus on the selection criteria for treatment of secondary immunodeficiency in cancer patients with IgG replacement therapy. Haematological malignancies such as CLL, MM and lymphoma are commonly associated with hypogammaglobulinemia. There is also an additional risk of iatrogenic secondary immunodeficiency from therapies used to treat these haematological cancers.

There is increasing demand for IgG treatment for a variety of disorders and since it is a blood product and can be subject to supply issues it is important to have clear guidance on the identification of cancer patients for treatment with IgG replacement therapy for secondary immunodeficiency.

2 Methodology

A group comprising of clinical experts from Haemato-oncology, Clinical Immunology and the NCCP (Appendix 1) was convened to develop this guidance which was circulated, to the Irish Haematology Society (IHS) and the Irish Association of Allergy and Immunology for comment. Feedback was collated and the final guidance document agreed.

3 Patient selection criteria

Before considering immunoglobulin replacement in new patients for the treatment of secondary immunodeficiency in cancer patients it should be recognised that antibiotic

[1] Please refer to current public health guidance on patient attendance as appropriate available at https://www.hpsc.ie/

prophylaxis can provide adequate protection to many patients with secondary antibody deficiency. Treatment with IgG should be reserved for those patients in whom antibiotic prophylaxis proves to be ineffective.

Patients meeting the selection criteria detailed below are recommended for consideration for treatment with IgG for secondary immunodeficiency (3,6, 7);

- Recurrent or severe bacterial infection despite continuous oral antibiotic therapy for 6 months (for patients post allogenic BMT please refer to their specialist centre for advice)
  OR
  Single severe life threatening infection

- Irreversible hypogammaglobinaemia, hypogammaglobinaemia associated with drugs, therapeutic monoclonals targeted at B cells and plasma cells (rituximab and other anti-CD20, CD19 agents, daratumumab etc.) post-HSCT, Non Hodgkin Lymphoma, Chronic Lymphocytic Leukaemia, Multiple Myeloma or other relevant B-cell malignancy confirmed by haematologist;

AND

- IgG <4 g/L (excluding paraprotein)
- Documented failure of serum antibody response to unconjugated pneumococcal or other polysaccharide vaccine challenge if appropriate
- Infections that cannot be fully attributed to neutropenia

Not all of the above criteria may need to be fulfilled for an individual patient. Any clinician is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment.

Use of Ig post-CAR-T therapy in B-cell acute lymphoblastic leukaemia (B-ALL)

- Because of the severity of B-cell aplasia and the longer time required for reconstitution, it is anticipated that virtually all patients (children and adults) with B-ALL will initially require Ig replacement following CAR-T cell therapy. As with the use of Ig post-CART therapy in B-cell lymphoma, continued use of IV Ig should be reviewed at regular intervals based on B-cell recovery, serum immunoglobulins and burden of infection

Use of Ig post-CAR-T cell therapy in B-cell lymphoma

- The need for immunoglobulin replacement in patients receiving CART cell therapy for B-cell lymphoma is variable ranging between 31% to 64% in published studies

highlighting faster B-cell recovery in this group in contrast to patients with B-cell acute lymphoblastic leukaemia

3.1 Specific exclusion criteria

It is important to carry out benefit-risk analyses in certain patient groups: patients at high risk of thromboembolism (hypertension, diabetes, smoking, hypercoagulable states) should be counselled regarding the prothrombotic risks of IgG.
IgA deficiency is no longer considered a contra-indication to the use of IgG.

4 Dosing Recommendations

The recommended dose for secondary immunodeficiency is 0.4–0.6g/kg/month modified to achieve an IgG trough level determined on an individualised basis considering co-morbidities and which would exceed at least the lower limit of the age-specific and method specific serum IgG reference range (check with local laboratory).
Doses are based on bodyweight and may require adjustment in underweight or overweight patients.
A number of licensed IgG products are available in Ireland. Product selection should be guided by local hospital formulary. The Summary of Product Characteristics (SmPC) for individual products is available at www.hpra.ie or www.ema.europa.eu and should be consulted to determine the recommended infusion and administration instructions. Currently licensed IgG products in Ireland can be divided into:

i) Intravenous products
ii) Subcutaneous products
iii) Hyaluronidase-facilitated subcutaneous products

These products have shown similar efficacy in terms of protection against infection however they are not identical with differences in properties such as IgA content, pH, additives (stabilisers), sodium content and osmolality due to different manufacturing methods. These differences could lead to differences in tolerability and adverse effects. Therefore, once a patient is established on a specific IgG product, this should not be changed to a different product in the absence of a clinical reason, without consultation with their clinician (5). However it is not uncommon for a small number of patients to be intolerant of any individual IgG product, but tolerate others. Therefore it is important that hospitals have alternative product(s) available or have secured an alternative supply of IgG product.

4.1 Monitoring

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Consideration should be given to the use of the lowest effective dose. The assessment of response to IgG is not solely dictated by the IgG level but on an overall clinical assessment of the patient's wellbeing and in particular, infection frequency and severity. An increase in dose may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free

- Annual reviews of treatment are recommended. If there are signs of recovery of humoral immunity (rising IgG, IgM or IgA levels) reduction of dose/cessation of therapy may be considered.

5 Appendix 1: Members of the Guidance Development Group

Role in group	Name and professional title
Consultant Haematologist (IHS representative)	Dr Anne Fortune, Consultant Haematologist, Mater Misericordiae University Hospital
Consultant Immunologist	Dr Mary Keogan, Consultant Immunologist, Beaumont Hospital
NCCP	Ms Patricia Heckmann, Assistant National Director, NCCP & Chief Pharmacist Dr Clare Meaney, NCCP, Senior Pharmacist Ms Helena Desmond, NCCP, Senior Pharmacist

6 References

1. Na et al. Current clinical practice and challenges in the management of secondary immunodeficiency in haematological malignancies. Eur J Haematol. 2019 Jun;102(6):447-456
2. Edgar et al. Prescribing Immunoglobulin Replacement Therapy for Patients With Non-classical and Secondary Antibody Deficiency: An Analysis of the Practice of Clinical Immunologists in the UK and Republic of Ireland. J Clin Immunol. 2018 Feb;38(2):204-213
3. Jolles et al, An international Delphi consensus building approach to patient assessment and use of immunoglobulin treatment for secondary immune

deficiencies in haematological malignancy. EHA Library. 06/12/20; 297829; PB1913, available at https://library.ehaweb.org/eha/2020/eha25th/297829/michael.albert.an.international.delphi.consensus.building.approach.to.patient.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Ddelphi+consensus

4. Jolles S. Subcutaneous and intramuscular immune globulin therapy UptoDate 20/12/2018. Accessed 10/04/2020.
5. Immunoglobulin Replacement Therapy for Primary Antibody Deficiency Model of Care (National Clinical Programme for Pathology) Available at https://www.hse.ie/eng/about/who/cspd/ncps/pathology/resources/immunoglobulin-replacement-therapy-primary-antibody-deficiency-moc.pdf
6. Department of Health guidelines (2nd edition update; July 2011) https://www.uhs.nhs.uk/Media/SUHTExtranet/TrustMedicinesFormulary/Forms/DH-IVIg-approved-indications-Full-Guidance-July-2011.pdf
7. Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig) England, 2021 Available at https://www.england.nhs.uk/wp-content/uploads/2021/12/cpag-policy-for-therapeutic-immunoglobulin-2021-update.pdf