Secondary immunodeficiency associated with haematological malignancies

SECONDARY IMMUNE DEFICIENCY

Improving infection outcomes and preventing infections with immunoglobulin replacement therapy (IgRT)

SECONDARY IMMUNE DEFICIENCY

Objectives of this module

SECONDARY IMMUNE DEFICIENCY

- To present data on the efficacy of IgRT in SID in haematological malignancies
- To present data on the tolerability of IgRT in SID in haematological malignancies
- To describe the administration routes of IgRT
- To describe the published recommendations for IgRT use

IgRT, immunoglobulin replacement therapy; SID, secondary immunodeficiencies.

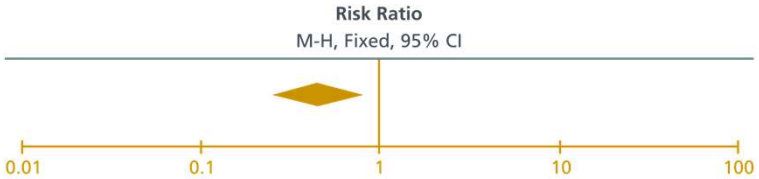
SECONDARY IMMUNE DEFICIENCY

Efficacy of immunoglobulin replacement therapy (IgRT)

IgRT decreases the risk of infection in CLL and MM

SECONDARY IMMUNE DEFICIENCY

Major Infection risk in CLL and MM patients with IgRT vs placebo or no treatment*



Study or Subgroup	Polyvalent IVIG Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		106		99	100.0%	0.45 [0.27, 0.75]
Total events	17		34			

Heterogeneity: $Chi^2 = 2.90$, df = 2 (P = 0.23); $I^2 = 31\%$

Test for overall effect: Z = 3.07 (P = 0.002)

Clinically documented infections in CLL and MM patients with IgRT vs placebo or no treatment*

Study or Subgroup	Polyvalent IVIG Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)		106		99	100.0%	0.49 [0.39, 0.61]
Total events	45		88			

Heterogeneity: $Chi^2 = 0.45$, df = 2 (P = 0.80); $I^2 = 0\%$

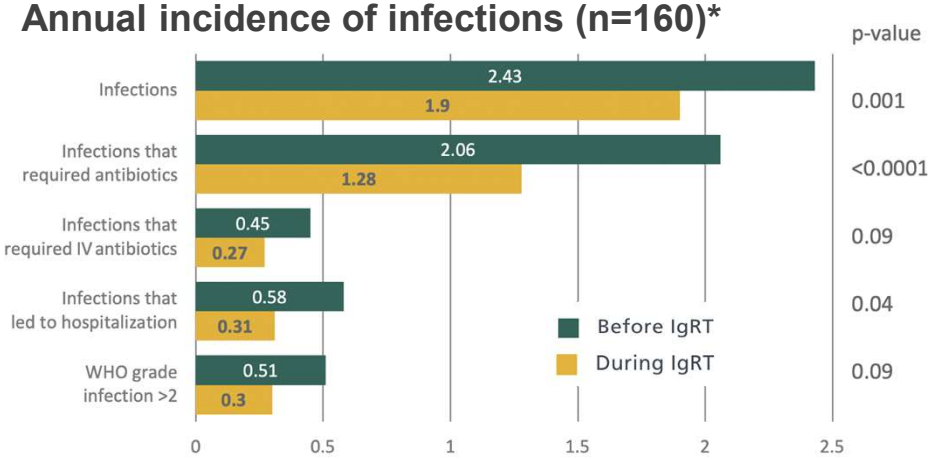
Test for overall effect: Z = 6.21 (P < 0.00001)

- The relative risk of major infections is decreased by 55% with IgRT in CLL and MM patients#
- No effect on mortality observed for IgRT compared with placebo or no treatment†

CI, confidence interval; HM, haematological malignancies; IgRT, immunoglobulin replacement therapy; IVIg, intravenous immunoglobulins; SID, secondary immunodeficiency
 # In patients with chronic lymphocytic leukaemia (CCL) and multiple myeloma (MM) compared to placebo or no treatment (data from 3 trials); †Data only from 2 trials available.
**This publication is a systematic review presenting data on the efficacy of IgRT for SID in haematological malignancies from 9 clinical trials, conducted between 1988 and 1996. All clinical trials involved CLL or MM patients, with the exception of one with both MM and low grade lymphoma. 7 trials compared polyvalent IVIG with control (i.e. placebo or no intervention), 2 trials compared different doses of IVIG and 2 trials were cross-over trials. In total 408 patients are included in this review (147 MM + 199 CLL + 62 CLL and MM)*
Raanani P. et al. Leuk Lymphoma 2009. 50:764.

IgRT decreases the risk of infection in HM

Annual incidence of infections (n=160)*



Patients characteristics*

	n
MM	54
CLL	54
aNHL	19
iNHL	29
HL	4

- The overall annual incidence of infections decreased by 22% with IgRT
- The annual incidence of infections during follow-up was independent of the previous management of HM (never treated, first-line of treatment, more than one line of treatment)
- This study supports the efficacy of IgRT in reducing the risk, frequency and severity of infections in HM associated with SID
- It suggests also a decrease in antibiotics consumption and a reduction in hospital admissions in SID patients

HM, haematological malignancies-associated; IgRT, immunoglobulin replacement therapy; HL, Hodgkin lymphoma; MM, multiple myeloma; CLL, chronic lymphocytic leukaemia; aNHL, aggressive non-Hodgkin lymphoma; iNHL, indolent non-Hodgkin lymphoma; SID, secondary immunodeficiencies; IVIg, intravenous immunoglobulin therapy; SCIg, subcutaneous immunoglobulin therapy.

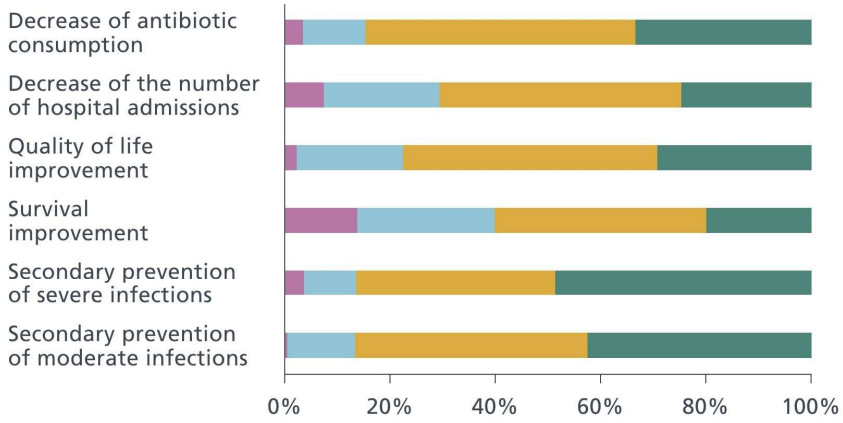
**This study was a non-interventional, multicenter, prospective French longitudinal study across 21 centers. The objective of the study was to document the efficacy and safety of IgRT in patient with HM-associated secondary immunodeficiency. 160 patients were followed up, Patients were followed-up for 8.7 ± 4.0 months. Patients were treated either with IVIg or SCIg and received similar monthly dose of about 400 kg/kg, in line with the recommendations*

Benbrahim O. et al. Hematology 2018. 24(1):173-182.

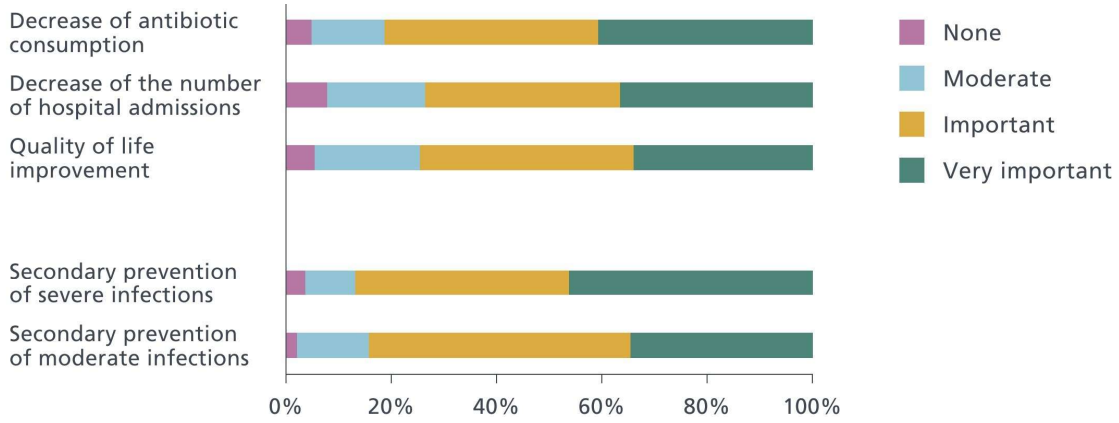
Physician’s expectations with IgRT in SID are satisfied

SECONDARY IMMUNE DEFICIENCY

Physicians’ expectations when prescribing immunoglobulin replacement therapy



Physician’s satisfaction during follow-up



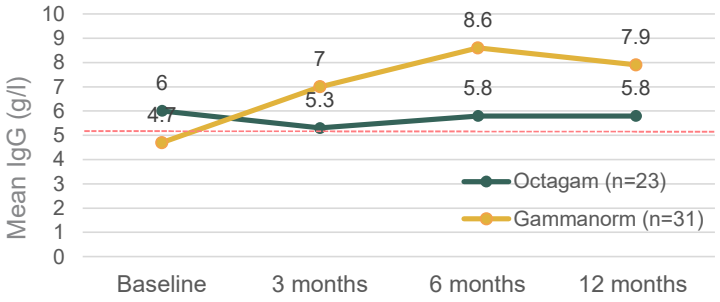
Physicians’ expectations when prescribing IgRT were largely met in terms of prevention of moderate or severe infections, decrease in the number of hospitalisations for sepsis and antibiotic consumption

SID, secondary immunodeficiency; IgRT, immunoglobulin replacement therapy; IVIg, intravenous immunoglobulin therapy; SCIg, subcutaneous immunoglobulin therapy
**This study was a non-interventional, multicenter, prospective French longitudinal study across 21 centers. The objective of the study was to document the efficacy and safety of IgRT in patient with HM-associated secondary immunodeficiency (SID). 231 patients were included and 160 were followed up: 54 multiple myeloma, 54 chronic lymphocytic leukaemia, 19 aggressive non-Hodgkin B-cell lymphoma, 29 indolent non-Hodgkin B-cell lymphoma and 4 Hodgkin disease. Patients were followed-up for 8.7 ± 4.0 months. Patients were treated either with IVIg or SCIg and received similar monthly dose of 400 kg/kg, in line with the recommendations.*
Benbrahim O. et al. Hematology 2018. 24(1):173-182.

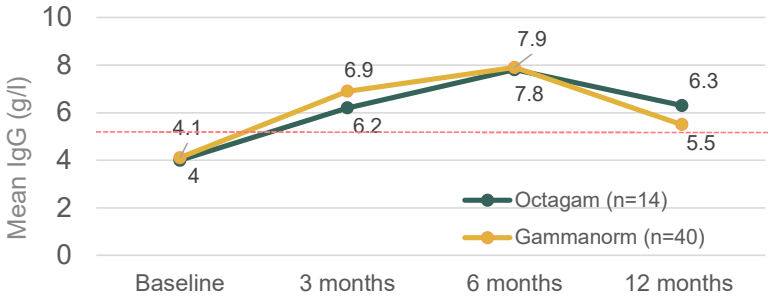
IgRT decreases the risk of infection in patients with HM*

SECONDARY IMMUNE DEFICIENCY

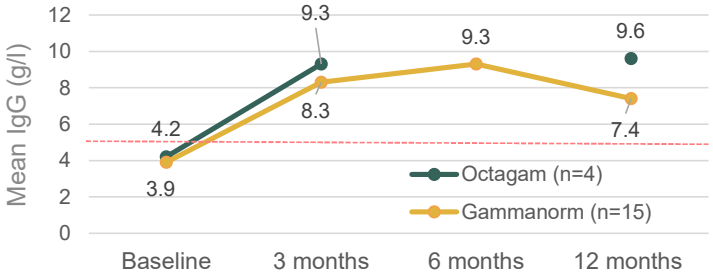
Multiple Myeloma patients#



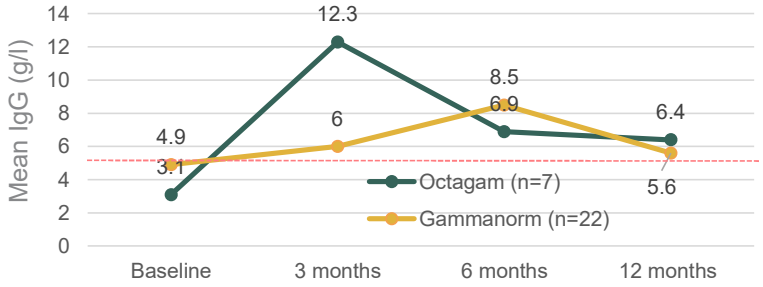
CLL patients#



Aggressive NHL patients#



Indolent NHL patients#



A higher increment was observed following the SC route but the difference did not reach statistical significance (p=0.10)

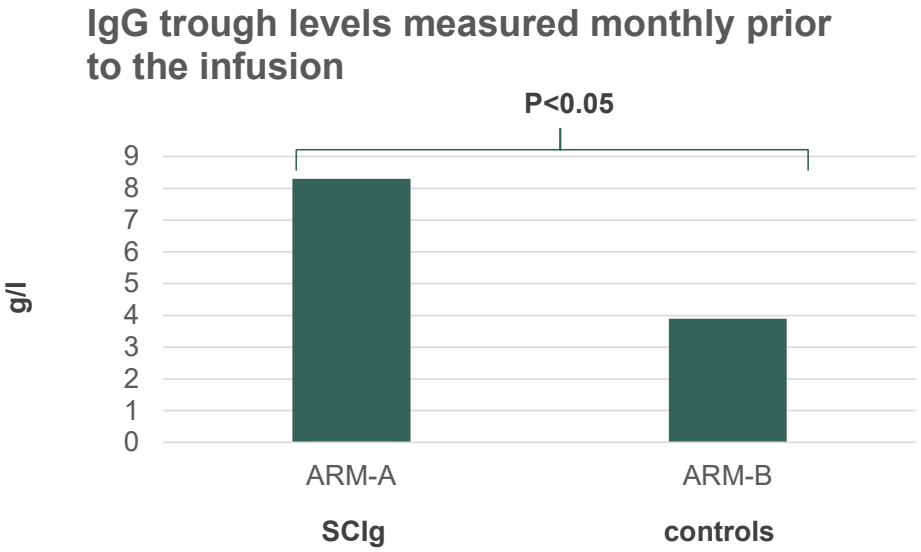
#A 12-month follow-up

**This study was a non-interventional, multicenter, prospective French longitudinal study across 21 centers. The objective of the study was to document the efficacy and safety of IgRT in patient with HM-associated secondary immunodeficiency (SID). 231 patients were included and 160 were followed up: 54 multiple myeloma, 54 chronic lymphocytic leukaemia, 19 aggressive non-Hodgkin B-cell lymphoma, 29 indolent non-Hodgkin B-cell lymphoma and 4 Hodgkin disease. Patients were followed-up for 8.7 ± 4.0 months. Patients were treated either with IVIg or SCIg and received similar monthly dose of 400 kg/kg, in line with the recommendations.*

CLL, chronic lymphocytic leukaemia; NHL: non-Hodgkin lymphoma; IgRT, Immunoglobulin replacement therapy; HM, haematological malignancies-associated

Data on file: Additional analysis of data from the study, September 2019

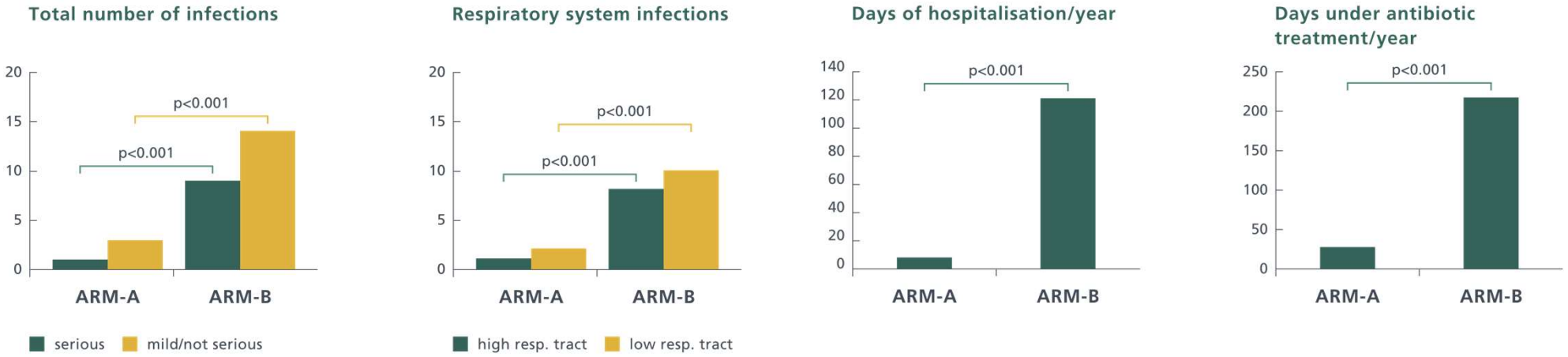
IgRT decreases the risk of infection in MM associated with hypogammaglobulinaemia



Median serum IgG levels were significantly higher in the SCIg group than in the control group

IgRT, immunoglobulin replacement therapy; MM, multiple myeloma; SCIg, subcutaneous immunoglobulin; IgG, immunoglobulin G
**A total of 46 patients with myeloma were enrolled at random: 24 of them were assigned to receive subcutaneous immunoglobulin and 22 were controls. The primary endpoint was the annual rate of severe infections in immunoglobulin-treated versus untreated patients.*
Vacca et al. Clin Immunol 2017.

IgRT decreases the risk of infection in MM associated with hypogammaglobulinaemia



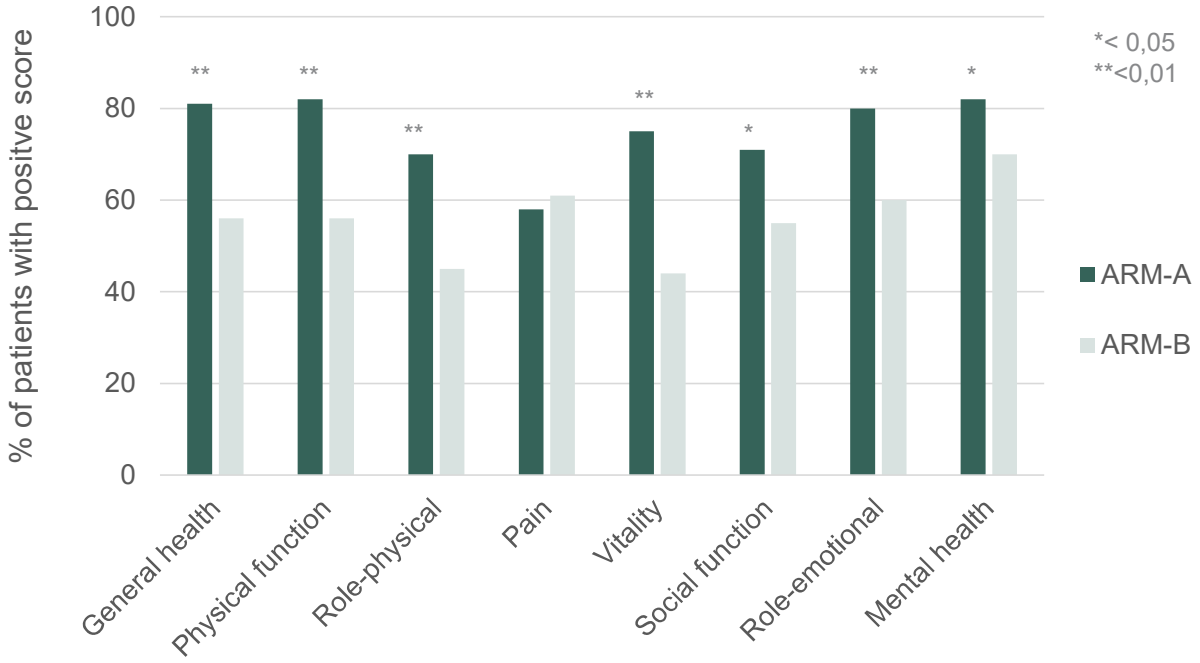
- SCIg significantly reduced the number of infections, the number of days of hospitalisation/year and the number of days of antibiotic use/year
- By reducing the rate of infections, prophylactic administration of SCIg improves both adherence to chemotherapy and health-related quality of life, and is cost-effective in reducing the need for hospitalisation and the use of antibiotics

IgRT, Immunoglobulin replacement therapy; MM, multiple myeloma; SCIg, subcutaneous immunoglobulin; IgG, immunoglobulin G
**A total of 46 patients with myeloma were enrolled at random: 24 of them were assigned to receive subcutaneous immunoglobulin and 22 were controls. The primary endpoint was the annual rate of severe infections in immunoglobulin-treated versus untreated patients.*
Vacca et al. Clin Immunol 2017.

IgRT decreases the risk of infection in MM associated with hypogammaglobulinaemia

SECONDARY IMMUNE DEFICIENCY

HR-QoL in MM patients with hypogammaglobulinaemia



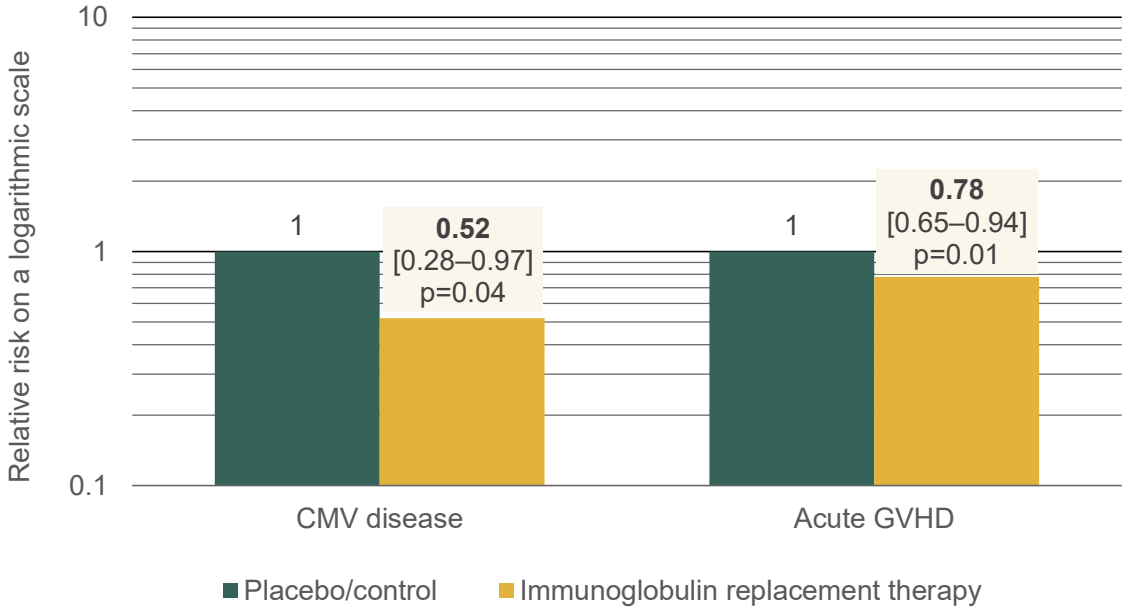
The quality of life related to health was significantly better in patients receiving subcutaneous immunoglobulin

IgRT, immunoglobulin replacement therapy; MM, multiple myeloma; HR-QoL, health-related quality of life
**A total of 46 patients with myeloma were enrolled at random: 24 of them were assigned to receive subcutaneous immunoglobulin and 22 were controls. The primary endpoint was the annual rate of severe infections in immunoglobulin-treated versus untreated patients.*
Vacca et al. Clin Immunol 2017.

IgRT decreases cytomegalovirus disease and acute graft versus host disease following haemapoietic stem cell transplantation*

SECONDARY IMMUNE DEFICIENCY

Relative risk of CMV disease (2 studies, n=167) and GVHD risk (8 studies, n=1097)



Immunoglobulin prophylaxis significantly decreased acute GVHD and CMV diseases

IgRT, immunoglobulin replacement therapy

**This publication is a systematic review and meta-analysis of 27 studies conducted of randomised controlled trials that assessed clinical outcomes of immunoglobulin prophylaxis versus placebo in haematopoietic stem cell transplant recipients. 3,934 patients were included. Study-relevant parameters were overall survival, transplant-related mortality, graft-versus-host disease [GVHD], veno-occlusive disease [VOD], interstitial pneumonitis, disease relapse, cytomegalovirus [CMV] infection and disease, non-CMV infection.*

Ahn H. et al. Transfusion 2018. Oct;58(10):2437-24522018.

SECONDARY IMMUNE DEFICIENCY

Tolerability of immunoglobulin replacement therapy (IgRT)

IVIg is very well-tolerated in SID

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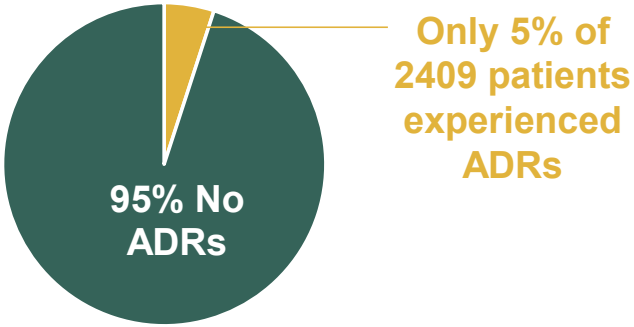
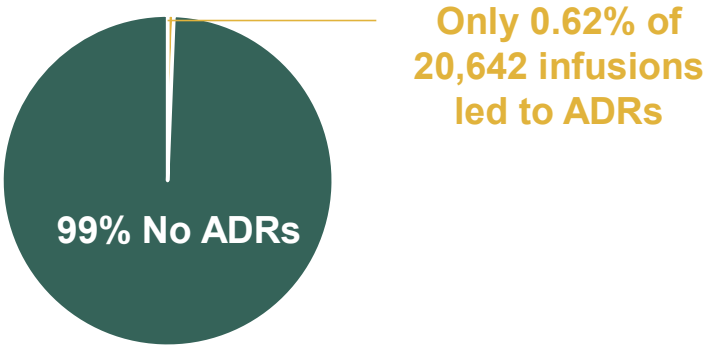
SID patients* treated with IVIg



ADRs occurring in infusions



This 10-year observational study demonstrates that IVIg is very well tolerated in routine clinical use

ADR, adverse drug reactions; IVIg, intravenous immunoglobulin; SID, secondary immunodeficiency.
**This study is a 10-year prospective observational study that evaluated the tolerability and safety of intravenous immunoglobulin therapy. SID in these patients is due to chronic lymphocytic leukaemia (728), multiple myeloma (339), bone marrow transplantation (566), other (776)*
Debes A. et al. Pharmacoepidemiol Drug Saf 2007. 16:1038.

Adverse drug reactions occurring in IVIg therapy are mild or moderate in severity

SECONDARY IMMUNE DEFICIENCY

The vast majority of ADRs (87%) occurring with IVIg in SID are mild or moderate*

Most frequent ADRs:

- Chills
- Headaches
- Back pain
- Hypersensitivity
- Nausea
- Dyspnoea
- Fatigue

ADR, adverse drug reactions; IVIg, intravenous immunoglobulin; SID, secondary immunodeficiency.
**A total of 210 ADRs were observed in 2,397 patients, of which 1,368 of them were treated for SID.*
Frenzel W. et al. Int J Clin Pharmacol Ther 2016. 54:847.

SECONDARY IMMUNE DEFICIENCY

Administering immunoglobulin replacement therapy (IgRT)

IgRT can be administered intravenously or subcutaneously

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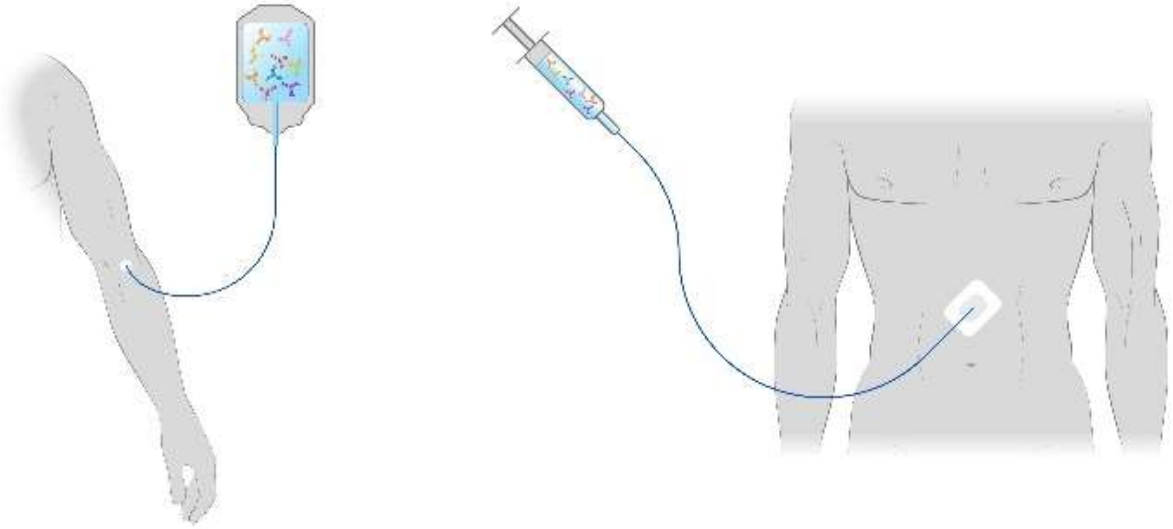
- Efficacy is similar between IVIg and SCIg

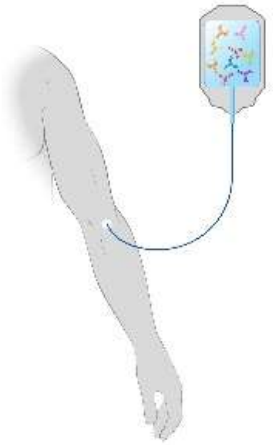


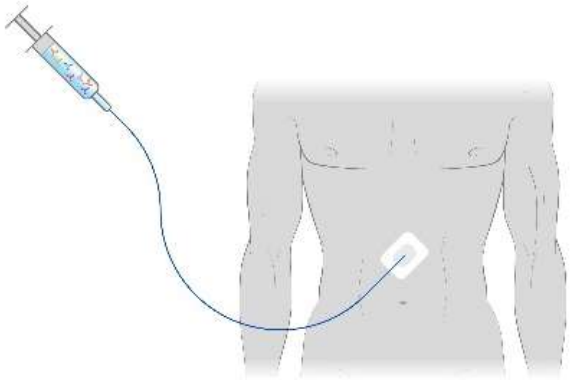
- Patient preference may be a key consideration when deciding on administration route

IgRT, immunoglobulin replacement therapy; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.

Agostini C. et al. Expert Rev Clin Immunol 2016. 12:921
Kerr J. et al. Int J Infect Dis 2014. 5:629.

IgRT administration: IVIg vs SCIg





	IVIg	SCIg
Treatment interval	Monthly	Weekly
Place of therapy	Often hospital-based	Often home-based
Pharmacokinetics of IgG	High peak serum Ig level	Steady IgG levels

Ig, immunoglobulin; IgRT, immunoglobulin replacement therapy; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.

Agostini C. et al. Expert Rev Clin Immunol 2016. 12:921; Kerr J. et al. Int J Infect Dis 2014. 5:629; Spadaro G. et al. Clin Immunol 2016. 166-7:103; Windegger T. M. et al. Transfus Med Rev 2017. 31:45.

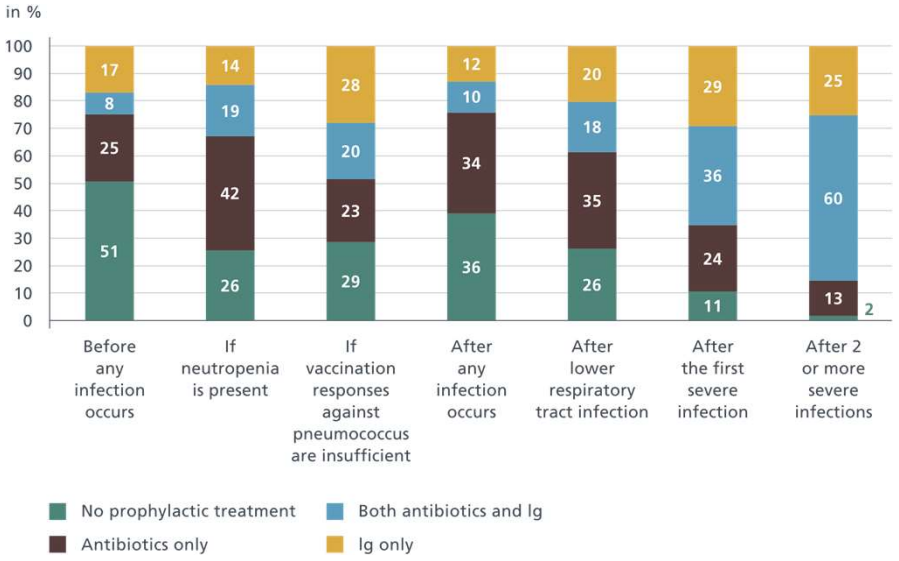
Current clinical practice and challenges in the management of SID in haematological malignancies

SECONDARY IMMUNE DEFICIENCY

- An international online survey of 230 physicians responsible for the diagnosis of SID and the prescription of IgRT in patients with haematological malignancies was conducted.
- Results showed that serum immunoglobulin was measured in 83% of patients with multiple myeloma, 76% with chronic lymphocytic leukaemia, and 69% with non-Hodgkin lymphoma.
- Most physicians (85%) prescribed IgRT after ≥2 severe infections
- In Italy, Germany, Spain, and the USA, immunoglobulin use was above average in patients with hypogammaglobulinaemia, while in the UK considerably fewer patients received IgRT
- The use of subcutaneous immunoglobulin was highest in France (34%)

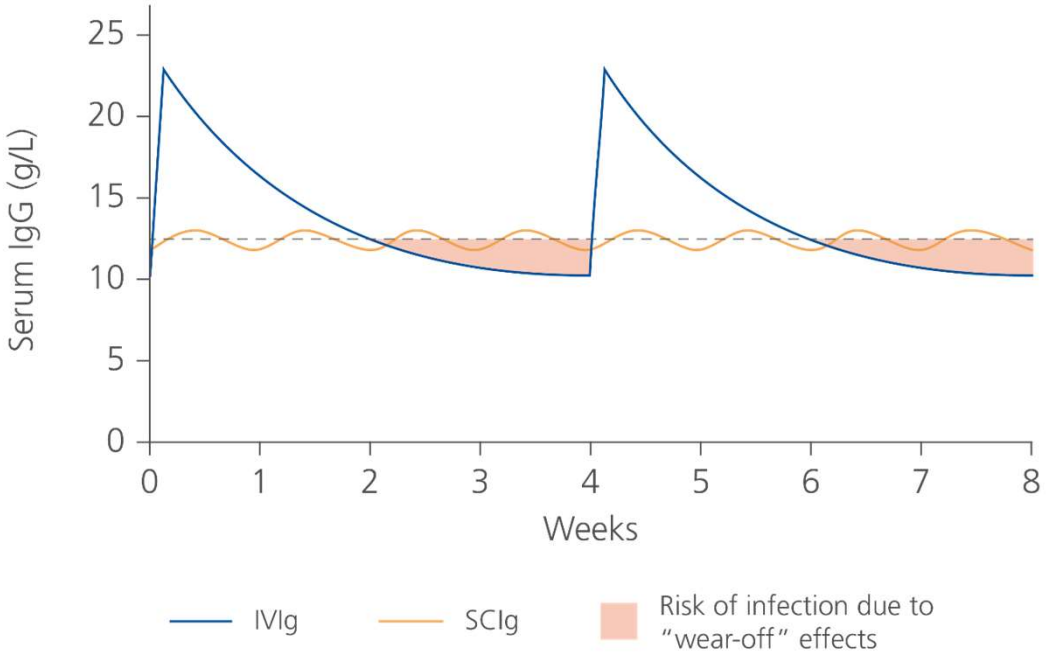
Infection prophylaxis across countries in patients with hypogammaglobulinaemia

(USA [N = 50], Canada, UK, France, Italy, Spain, and Germany [N = 30 each])



IgRT, immunoglobulin replacement therapy; SID, secondary immunodeficiency; Ig, immunoglobulin
Na et al., Eur J. Haematol. 2019; 102:447–456.

SCIg results in constant serum IgG levels*



- High peak IgG concentration might increase incidence of systemic and severe AEs
- Stable IgG concentration confers constant infection protection
- Infection risk increases with falling IgG concentration

AEs, adverse events; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.
**IgRT use in primary immunodeficiency.*
Jolles S. et al. Clin Exp Immunol 2015. 179:146.

Tool for decision-making to start IgRT in HM-associated SID

IgRT, immunoglobulin replacement therapy; HM, haematological malignancies-associated; SID, secondary immunodeficiencies.

Tool for decision-making to start IgRT in HM-associated SID

SECONDARY IMMUNE DEFICIENCY

The choice of antibiotic prophylaxis and/or IgRT as a treatment in patients with antibody deficiency should be based on the evaluation of the clinical and immunological features

- Review of the patient's history: tolerability and drug-resistance of antibiotics
- Assessment of the risk factors for developing secondary antibody deficiency
- Evaluation of serum IgG levels and specific antibody levels

IgRT, immunoglobulin replacement therapy; HM, haematological malignancies-associated; SID, secondary immunodeficiencies; Ig, immunoglobulin
Agarwal S. et al. Allergy Clin Immunol 2013. 131(6): 1699–1701.

Tool for decision-making to start IgRT in HM-associated SID

Suggested decisional score to initiate IgG therapy in patients with hypogammaglobulinaemia

	Point value	0	1	2	3	4	5
Laboratory	IgG (mg/dl)	600	350-599		150-349		0-149
	IgA (mg/dl)	normal			reduced		≤10
	IgM (mg/dl)	normal			reduced		≤15
	Diphteria or tetanus	protective					nonprotective
	% of protective pneumococcal serotype	≥50%			20-49%		0-19%
Clinical history	Pneumonia / lifetime	none	1	2	3	4	Five or more
	Upper respiratory infections/year	none	1	2	3		>3
	Antibiotic courses/year						
	Autoimmune disease-ITP, AIHA, or other	none			present		≥5 or prophylactic
	Sepsis / Meningitis / Osteomyelitis / Empyema / Septic Arthritis	none					present
	Splenomegaly or splenectomy	none			present		
	Lymphadenopathy	none			present		
	Infectious diarrhea (excluding clostridium difficile)	none			present		
	Malabsorption, chronic gastroenteritis, inflammatory bowel-like disease	none			present		
	Weight less/ failure to thrive	none			present		
	Hospitalisations / % years	none	1	2	3	4	present
Other	Pulmonary function tests	normal	FEV1/ FVC or TLC < 80% predicted		FEV1/ FVC or TLC < 70% predicted		FEV1/ FVC or TLC < 60% predicted
	Bronchietasis	none					present

This score highlights the relevance of immunoglobulin serum levels, vaccine responses, infectious events and bronchiectasis finding

AIHA, Autoimmune haemolytic anaemia; FVC, forced vital capacity; ITP, idiopathic thrombocytopenic purpura; TLC, total lung capacity. IgRT, immunoglobulin replacement therapy; HM, haematological malignancies-associated; SID, secondary immunodeficiencies

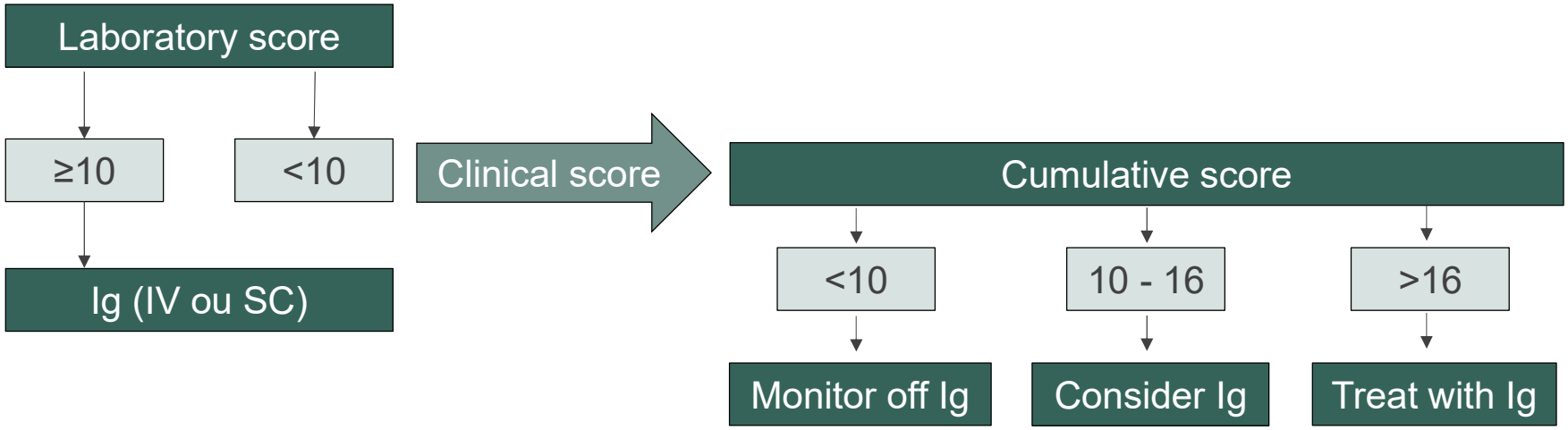
Agarwal S. et al. Allergy Clin Immunol 2013. 131(6): 1699–1701.

Tool for decision-making to start IgRT in HM-associated SID

Suggested decisional score to initiate IgG therapy in patients with hypogammaglobulinaemia

SECONDARY IMMUNE DEFICIENCY

Scoring decision tree



Ig, immunoglobulin; IV, intravenous; SC, subcutaneous; IgRT, immunoglobulin replacement therapy; HM, haematological malignancies; SID, secondary immunodeficiencies.
Agarwal S. et al. Allergy Clin Immunol 2013. 131(6): 1699–1701.

Recommendations for immunoglobulin replacement therapy (IgRT) use

IgRT, immunoglobulin replacement therapy

Several guidelines exist for IgRT use in haematological malignancies

SECONDARY IMMUNE DEFICIENCY

These guidelines include those from:

- European Medicine Agency (EMA)
- Work Group Report of the American Academy of Allergy, Asthma & Immunology
- IVIg Hematology and Neurology Expert Panel, Canada
- Department of Health, UK
- British Committee for Standards in Haematology
- European Multiple Myeloma Network
- CIBMTR, NMDP, EBMT, ASBMT, CBMTG, IDSA, SHEA, AMMI, and CDC

ASBMT, American Society of Blood and Marrow Transplantation; AMMI, Association of Medical Microbiology and Infectious Diseases Canada; CBMTG, Canadian Blood and Marrow Transplant Group; CDC, Centers for Disease Control and Prevention; CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Blood and Marrow Transplant Group; IDSA, Infectious Diseases Society of America; IgRT, immunoglobulin replacement therapy; IVIg, intravenous immunoglobulin; NMDP, National Marrow Donor Program; SHEA, Society for Healthcare Epidemiology of America.

Indication for IgRT use in SID

SECONDARY IMMUNE DEFICIENCY

New EMA guidelines on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) released in 2018

4.1 Therapeutic indications

Replacement therapy in adults, and children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)** or serum IgG level of <4 g/l

These guidelines now include a broad SID indication covering e.g. besides CLL and multiple myeloma (MM), also patients with other haematological malignancies and/or those treated with B cell–depleting therapies, and hypogammaglobulinaemia following bone marrow transplantation and solid organ transplantation

IgRT, immunoglobulin replacement therapy; SID, secondary immunodeficiencies; EMA, European Medicines Agency; SmPC, summary of product characteristics; CLL, chronic lymphocytic leukaemia; Ig, immunoglobulin; PSAF = proven specific antibody failure

EMA. Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg). 2018.

Guidelines for IgRT use in haematological malignancies and haematopoietic stem cell transplantation

SECONDARY IMMUNE DEFICIENCY

Work Group Report of the American Academy of Allergy, Asthma & Immunology

Indication in HM

In CLL patients with recurrent bacterial infections in presence of HGG and subprotective levels of specific antibody production following immunisation to diphtheria, tetanus or pneumococcal infection

In MM patients with recurrent bacterial infections in presence of subprotective levels of specific antibody production following immunisation to diphtheria, tetanus or pneumococcal infection

Dose and administration route in HM

Guidance not specified

Indications in HSCT

May be considered for:

- Patients with chronic GVDH and recurrent serious bacterial infections with proven antibody production defect

Not recommended for (not enough evidence):

- Cord blood stem cell transplantation for SID

CLL, chronic lymphocytic leukaemia; GVHD, graft versus host disease; HGG, hypogammaglobulinaemia; HM, haematological malignancies; HSCT, haematopoietic stem cell transplant; IgRT, immunoglobulin replacement therapy; MM, multiple myeloma; SID, secondary immunodeficiency.

Perez E. E. et al. J Allergy Clin Immunol 2017. 139:S1.

Guidelines for IgRT use in haematological malignancies and haematopoietic stem cell transplantation

SECONDARY IMMUNE DEFICIENCY

IVIg Hematology and Neurology Expert Panel, Canada

Indication in HM

In adults with HGG or dysfunctional gammaglobulinaemia and either:

- A recent life-threatening infection caused by low Ig serum levels
- Recurring clinically significant infections caused by low Ig serum levels

In children not recommended for routine use, except with HM associated HGG and history of severe invasive infection or recurrent sinopulmonary infections

Dose recommendation in HM

0.4 g/kg every 3 weeks with re-evaluation every 4–6 months

Indications in HSCT

For routine use, IgRT in HSCT is not recommended

CLL, chronic lymphocytic leukaemia; GVHD, graft versus host disease; HGG, hypogammaglobulinaemia; HM, haematological malignancies; HSCT, haematopoietic stem cell transplant; IgRT, immunoglobulin replacement therapy; MM, multiple myeloma; SID, secondary immunodeficiency; IVIg, intravenous Immunoglobulin.

Anderson D. et al. Transfus Med Rev 2007. 21:S9.

Guidelines for IgRT use in haematological malignancies and haematopoietic stem cell transplantation

SECONDARY IMMUNE DEFICIENCY

Department of Health, United Kingdom

Indication in HM

HGG associated with NHL, CLL, MM or other B-cell malignancies and either:

- Recurrent or severe bacterial infection despite oral antibiotic therapy for 3 months
- IgG <5 g/L
- Proven failure of specific antibody response to unconjugated pneumococcal or other polysaccharide vaccine

Dose recommendation in HM

0.4 g/kg/month

Can be modified to achieve Ig trough level of at least lower limit of age-specific serum IgG reference range

Indications in HSCT

Not recommended for HSCT in SID

CLL, chronic lymphocytic leukaemia; HGG, hypogammaglobulinaemia; HM, haematological malignancies; Ig, immunoglobulin; IgRT, immunoglobulin replacement therapy; HSCT, haematopoietic stem cell transplant; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; SID, secondary immunodeficiency.

Department of Health. Clinical guidelines for Immunoglobulin Use. 2nd edition. 2011.

Guidelines for IgRT use in Chronic Lymphocytic Leukaemia

SECONDARY IMMUNE DEFICIENCY

British Committee for Standards in Haematology

Indication

Recurrent or severe bacterial infection despite prophylactic antibiotic therapy

Serum IgG <5 g/L (excluding a paraprotein)

Dose and administration route

Initial dose: 0.4 g/kg

- IV: every 3–4 weeks
- SC: Weekly

Adjust for clinical response

Aim for trough level 6–8 g/L after 4 months

- Higher trough levels may be beneficial with co-morbidities

Monitoring

Review patients regularly

Record infection incidence and severity, antibiotic sensitivity

Phlebotomy: Annual HBsAg and HCV PCR screening, serum IgG every 3–4 months

Further management

If serious or recurrent infections develop despite antimicrobial prophylaxis and IgRT, manage in conjunction with a microbiologist, infection disease specialist, or immunologist

Stop IgRT treatment after 1 year if no improvement in infection frequency of severity

CLL, chronic lymphocytic leukaemia; HBsAg, hepatitis B surface antigen; HCV PCR, hepatitis C virus polymerase chain reaction; Ig, immunoglobulin; IgRT, immunoglobulin replacement therapy; IV, intravenous; SC, subcutaneous.

Oscier D. et al. Br J Haematol 2012. 159:541.

Guidelines for IgRT use in Multiple Myeloma

SECONDARY IMMUNE DEFICIENCY

European Multiple Myeloma Network

Indication

Not recommended for routine prophylaxis of bacterial infection

May be considered for subset of patients with severe, recurrent bacterial infections and hypogammaglobulinaemia

Dose and administration route

Guidance not specified

Monitoring

Guidance not specified

IgRT, immunoglobulin replacement therapy.
Terpos E. et al. Haematologica 2015. 100:1254.

Guidelines for IgRT use with haematopoietic stem cell transplantation: within first 100 days following HSCT

SECONDARY IMMUNE DEFICIENCY

CIBMTR, NMDP, EBMT, ASBMT, CBMTG, IDSA, SHEA, AMMI, and CDC

Indication

Not recommended for:

- Routine prophylaxis of bacterial infection
- Patients with IgA deficiency should not receive standard Ig products

May be considered for:

- Prevention of bacterial infection in patients with severe hypogammaglobulinaemia (IgG <400 mg/dL)

Monitoring

Check serum IgG levels every 2 weeks

Dose and administration route

Adults and adolescents: IVIg, 500 mg/kg/week

Paediatric: IVIg, 400 mg/kg/month

Individualise dose and frequency to maintain trough serum IgG >400 mg/dL*

**IVIg half-life among HSCT recipients (1–10 days) is shorter than the IVIg half-life among healthy adults (18–23 days).*

ASBMT, American Society of Blood and Marrow Transplantation; AMMI, Association of Medical Microbiology and Infectious Diseases Canada; CBMTG, Canadian Blood and Marrow Transplant Group; CDC, Centers for Disease Control and Prevention; CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Blood and Marrow Transplant Group; HSCT, haematopoietic stem cell transplant; IDSA, Infectious Diseases Society of America; Ig, immunoglobulin; IgRT, immunoglobulin replacement therapy; IVIg, intravenous immunoglobulin; NMDP, National Marrow Donor Program; SHEA, Society for Healthcare Epidemiology of America.

Tomblyn M. et al. Biol Blood Marrow Transplant 2009. 15:1143.

Guidelines for IgRT use with haematopoietic stem cell transplantation: over 100 days following HSCT

SECONDARY IMMUNE DEFICIENCY

CIBMTR, NMDP, EBMT, ASBMT, CBMTG, IDSA, SHEA, AMMI, and CDC

Indication

Not recommended for:

- Routine prophylaxis of bacterial infection without severe hypogammaglobulinaemia
- Patients with IgA deficiency should not receive standard Ig products

May be considered for:

- Prevention of bacterial infection in patients with severe hypogammaglobulinaemia (IgG <400 mg/dL)

Monitoring

Guidance not specified

Dose and administration route

IVIg: 500 mg/kg every 3–4 weeks

ASBMT, American Society of Blood and Marrow Transplantation; AMMI, Association of Medical Microbiology and Infectious Diseases Canada; CBMTG, Canadian Blood and Marrow Transplant Group; CDC, Centers for Disease Control and Prevention; CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Blood and Marrow Transplant Group; HSCT, haematopoietic stem cell transplant; IDSA, Infectious Diseases Society of America; Ig, immunoglobulin; IgRT, immunoglobulin replacement therapy; IVIg, intravenous immunoglobulin; NMDP, National Marrow Donor Program; SHEA, Society for Healthcare Epidemiology of America.

Tomblyn M. et al. Biol Blood Marrow Transplant 2009. 15:1143.

There are key indicators for IgRT use in SID

SECONDARY IMMUNE DEFICIENCY

These key indicators include:

Severe or recurrent bacterial infections

Ineffective antibiotic treatment

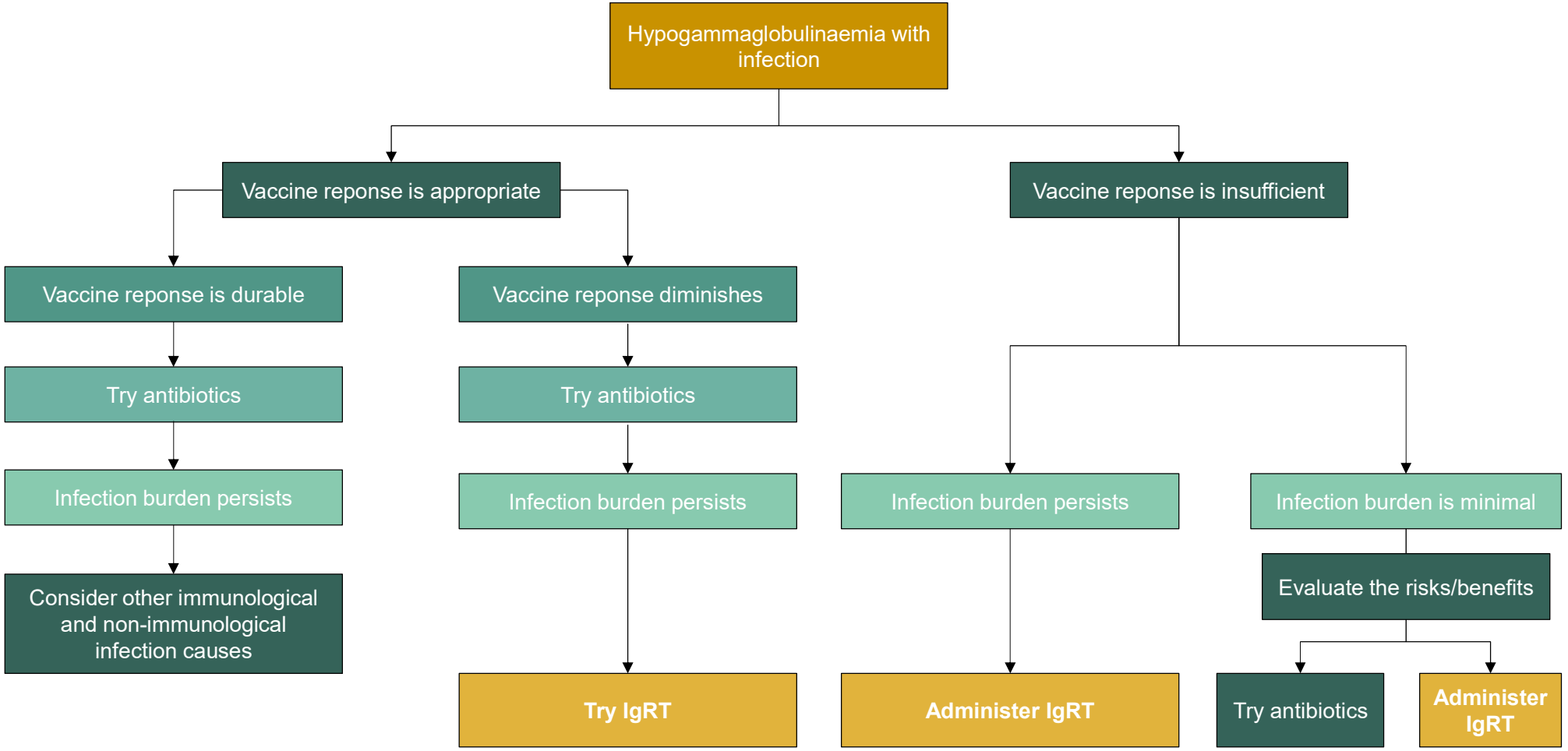
Proven specific antibody failure (PSAF)*

HGG: serum IgG level of <4 g/L

Ig, immunoglobulin; IgRT, immunoglobulin replacement therapy; HGG, hypogammaglobulinaemia; SID, secondary immunodeficiency.
**Failure to amount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.*
EMA. Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg). 2018.

IgRT should be initiated in the presence of HGG with infections and impaired immune response

SECONDARY IMMUNE DEFICIENCY



IgRT, immunoglobulin replacement therapy; HGG, hypogammaglobulinaemia. Flow chart adapted from Jolles S. et al. Clin Exp Immunol 2017. 188:333.

Conclusions

- IgRT is efficacious in immune compromised patients with haematological malignancies
  - Ig infusion can reduce infection risk and infection frequency (IV and/or Subcutaneous route)
- IgRT is very well-tolerated – adverse drug reactions are infrequent, and mainly mild or moderate
- IgRT can be administered subcutaneously or intravenously
- Evidence-based guidelines for use of IgRT in SID in HM are available

HM, haematological malignancies; IgRT, immunoglobulin replacement therapy; IVIg, intravenous immunoglobulin; SID, secondary immunodeficiency.

SECONDARY IMMUNE DEFICIENCY

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