Secondary Immunodeficiency in Multiple Myeloma

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July 2024

Background – Multiple Myeloma

- 2nd most common hematologic malignancy
- Precursor conditions: MGUS, SMM
- Therapeutic evolution results in extended disease control and survival
- Multiple therapeutics lines, usually involving combination regimens:
  - PIs
  - IMiDs
  - Chemotherapy
  - Corticosteroids
  - Monoclonal antibodies — anti CD38, slamf7
  - ADCs — BCMA
  - BisAbs — GPRC5D
  - CART — FcRH5

Immunosuppression in MM

- Disease related:
  - Dysfunction of B cells with hypogammaglobinemia
  - Disruption of global T-cell diversity
  - Alteration in the functional activity of dendritic, NK cells and alternative complement pathway
- Treatment related:
  - Neutropenia
  - T-cell exhaustion/ depletion
  - Mucosal/ dental damage
- Associated comorbidity
  - Renal failure
  - Immobility
- Host factors
  - age

Adapted from Raje et al. Lancet oncology 2022

Frequency of Hypogammaglobulinemia in Myeloma and precursor conditions

Disease	Median age at Diagnosis	Incidence Rates (per 100,000)	Prevalence (%)	Hypogammaglobulinemia Frequency (%)
MGUS	70[37]	60-120 at 50 years[33] 188-278 at 80 years[33]	1.7 at 50-59 years[35] 6.6 at >80 years[35]	25-29[35,36,38]
SMM	62-67[39,40]	0.4-0.9[39]	NR	45-83[34,41,42]
MM	69[24]	7.1[24]	0.8[24]	Up to 90[15,43]

- A population-based study* demonstrated that patients with MGUS have a significantly increased risk of bacterial (eg, pneumonia, endocarditis, meningitis), and viral (influenz and herpes zoster) infections compared with controls, higher risk with M-protein > 25 g/L

**Giart D et al. CLML. 2023 **Kristinsson SY et al. Haematologica* . 2012;97:854–858

Infections in Myeloma patients – *definitions*:*

- Severe infection - requires immediate or prolonged hospitalization, or emergency or intensive care treatment
- Persistent infection - caused by the same microbe, and which does not improve despite appropriate selection and duration of the anti-infective treatment
- Recurrent infection - clinically documented infections (such as sinusitis, pneumonia, or cellulitis) occurring after the resolution of the prior infection with appropriate anti-infective treatment

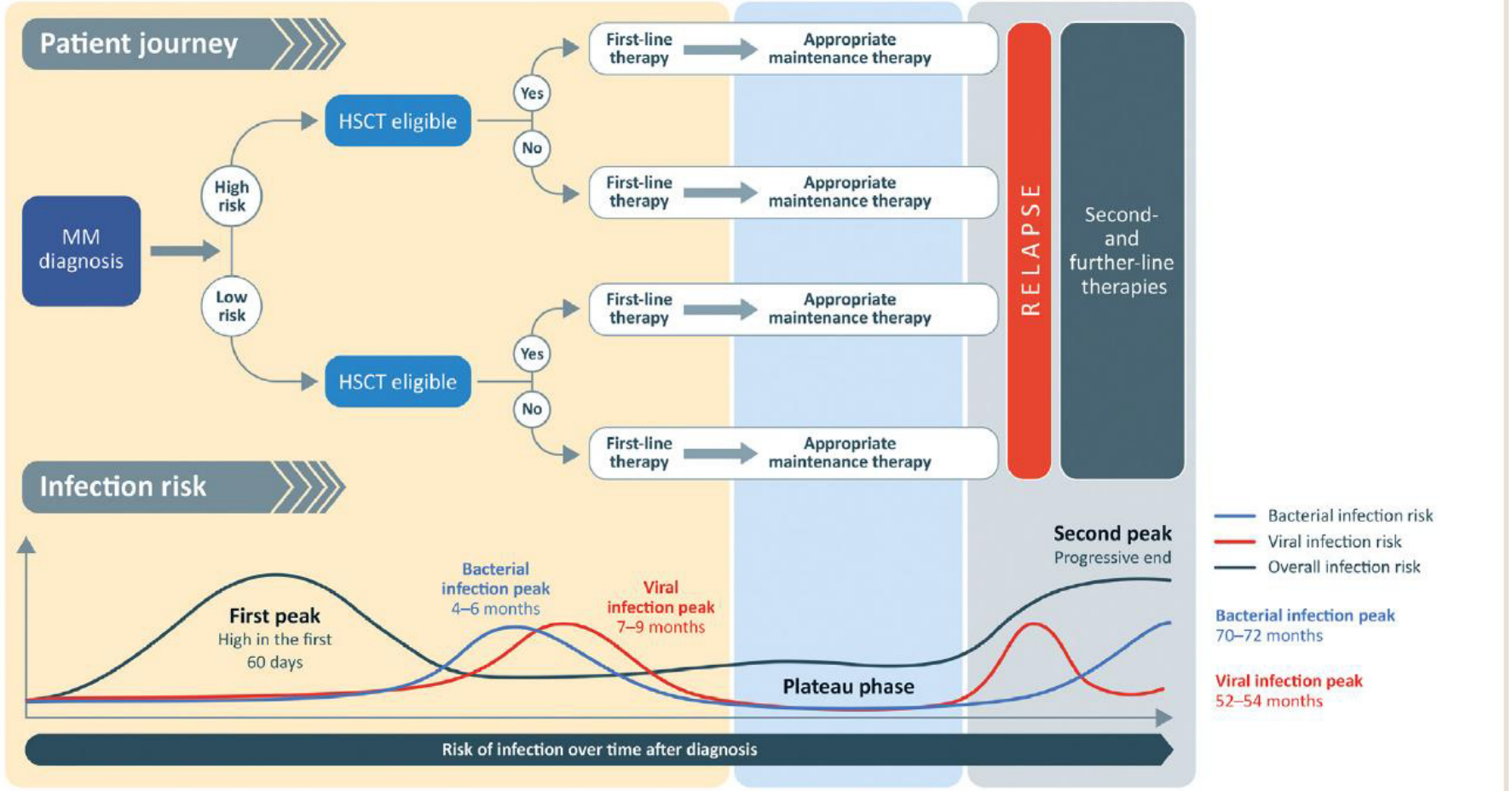
* Jolles et a;. *Eur J Haematol.* 2021;106:439–449

Infections are common in Myeloma pts & are associated with increased mortality

- UK retrospective study:
  - A 7-fold increase for infections vs matched controls
  - During 1st year since diagnosis: 11-fold increase for bacterial and 18-fold for viral infections
  - Overall survival was significantly shorter in patients with infection compared with those without infection
- US NIH study of 20% of nation hospital admissions (85K)
  - 47.8% of patients hospitalized with MM died with infections
  - 10% estimated to die before potential benefit from anti MM therapy

→ infections are a major cause of death in patients with MM

Infection risk peaks in a bimodal distribution throughout the MM disease



Risk factors for infections in MM

- Increasing age
- Disease stage (ISS stage [higher risk with later stages of disease])
- Disease status (relapsed/refractory higher risk than newly diagnosed)
- Number of prior treatment lines (1, 2, >3)
- Comorbidities (frailty, performance status, nutrition, diabetes mellitus, smoking, renal impairment, COPD)
- Use of B-cell targeting therapies
- CAR T therapy
- Severity of hypogammaglobulinemia (<4 g/L)
- Degree of antibody deficiency (hypogammaglobulinemia [only IgG decreased] vs panhypogammaglobulinemia [IgG, IgA, and IgM decreased])
- Prior infections and infection-related hospitalizations
- Poor response to vaccines

Abbreviations: CAR T = chimeric antigen receptor T-cell; COPD = chronic obstructive pulmonary disease; Ig = immunoglobulin; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; ISS = international staging system; MM = multiple myeloma; SAD = secondary antibody deficiency.

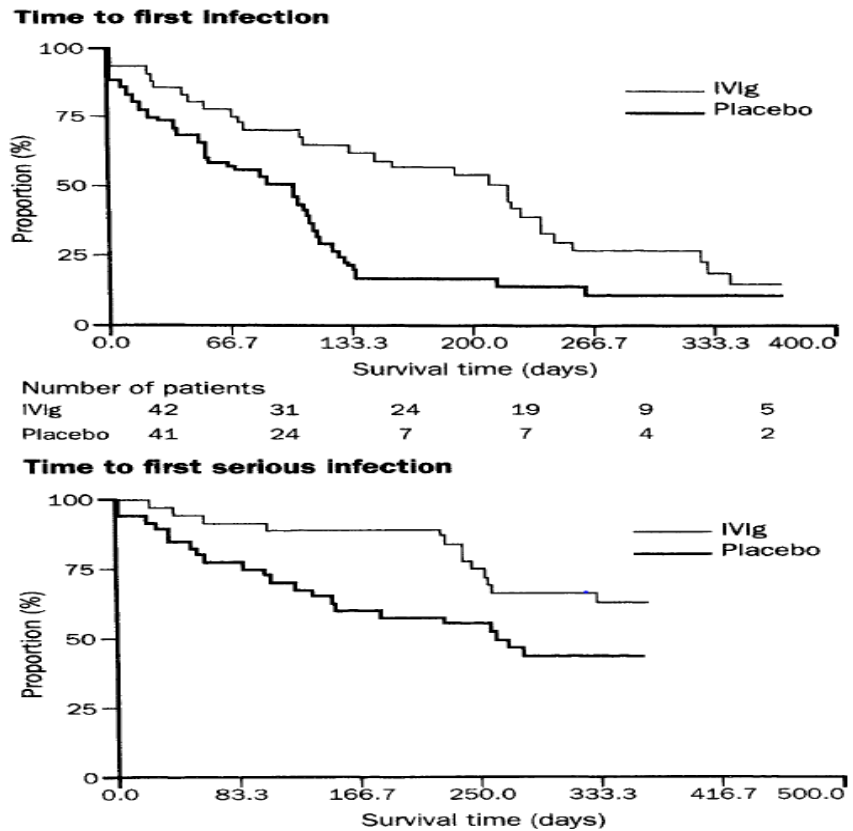
Infections are associated with increased risk for early mortality:

- Danish nationwide population-based myeloma database showed that in the first 180 days after diagnosis, 22% of patients (n = 330) died, with 50.9% (n = 212) of these deaths attributable to infection
- UK MRC trials - early mortality (≤60 days post- diagnosis) occurred in 10% of all patients with newly diagnosed MM; of which 45% were attributable to infection

Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma

*H M Chapel, M Lee, R Hargreaves, D H Pamphilon, A G Prentice, for the UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma**

	IVIg	Placebo	p (two tailed value)*
Septicaemia	0	3	0 045
Pneumonia	0	7	0 005
Chest infections (other than pneumonia)	6	18	0 0097
Urinary tract infections	8	5	ns
Skin sepsis/abscess/cellulitis	2	0	ns
PUO	2	0	ns
Other	1	5	ns
Total	19	38	



Lancet 1994; **343:** 1059–63

Received: 3 March 2023 | Revised: 23 April 2023 | Accepted: 15 May 2023
DOI: 10.1002/hon.3185

ORIGINAL ARTICLE

WILEY

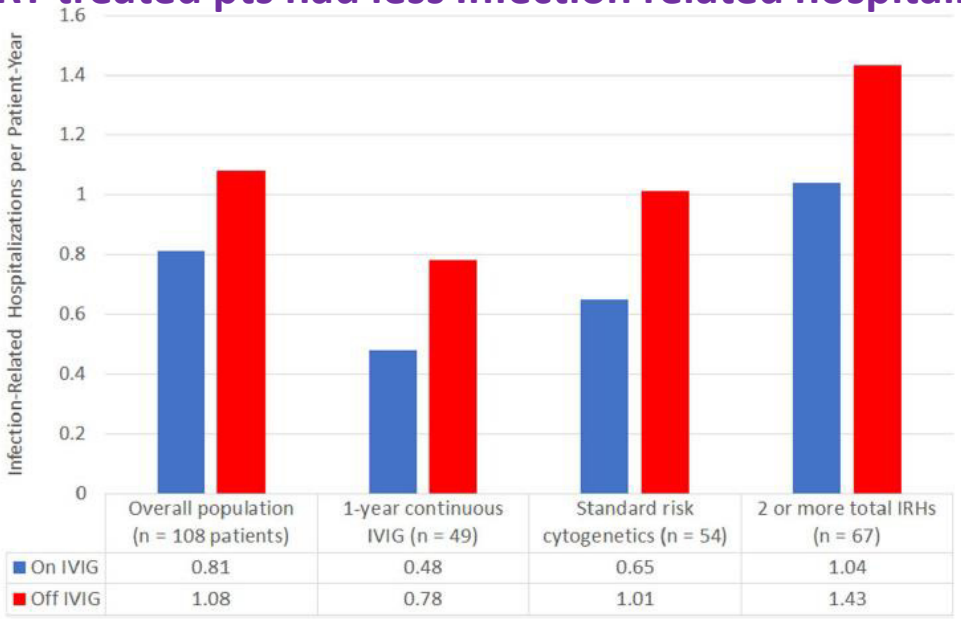
Intravenous immunoglobulin prophylaxis is associated with decreased rate of infection-related hospitalizations in multiple myeloma patients

Michael Sheu[1] | Sofia Molina Garcia[1] | Meera Patel[1] | Lauren Granat[1] | Louis Williams[2] | Jack Khouri[2] | Sherif Mossad[3] | Faiz Anwer[2] | Aneela Majeed[3]

[1]Cleveland Clinic, Internal Medicine,

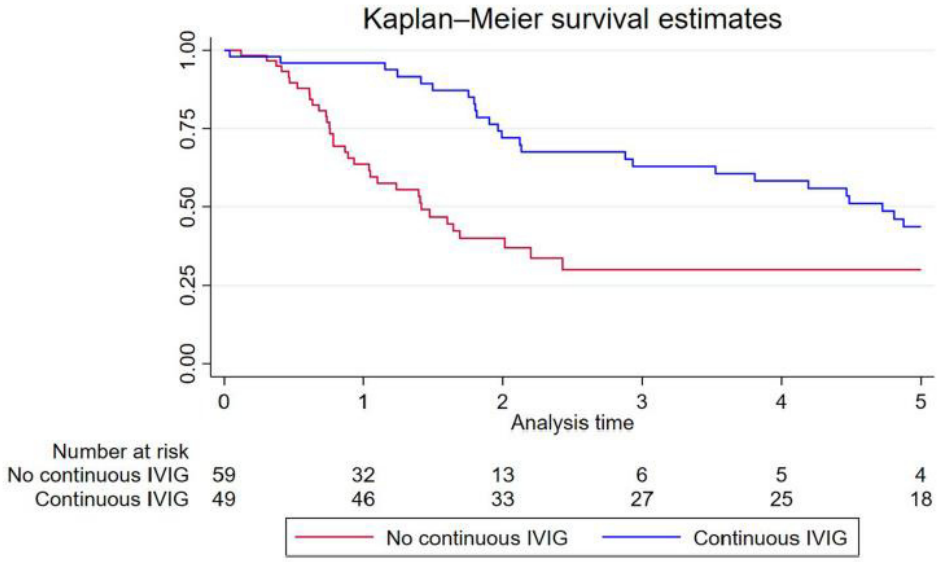
- Retrospective study of MM patients who received IVIG at Taussig Cancer Center between July 2009 and July 2021; N=108
- The primary endpoint was rate of infection-related ospitalizations (IRHs) per patient-year on-IVIG versus off-IVIG.

IgRT treated pts had less Infection related hospitalizations



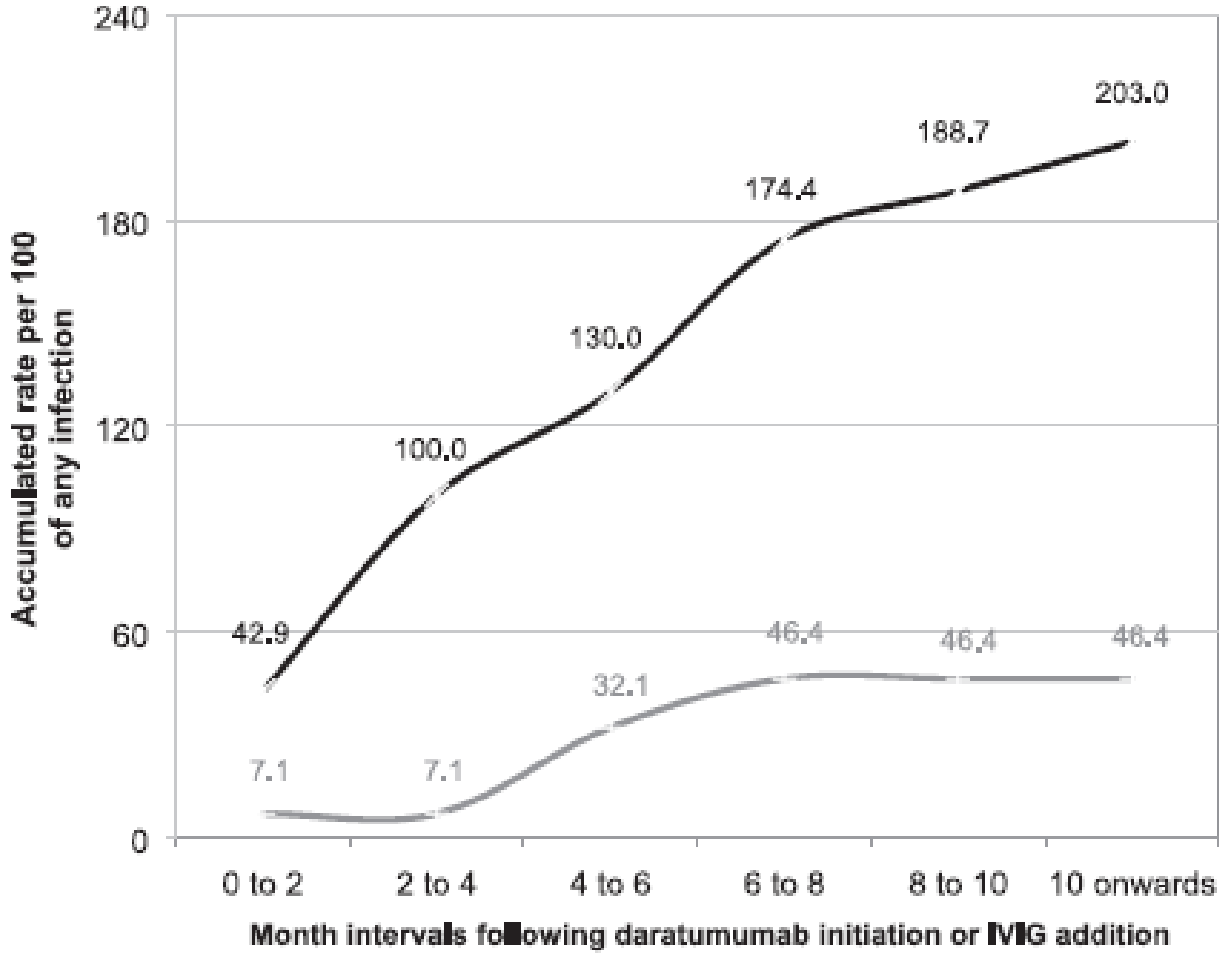
	Overall population (n = 108 patients)	1-year continuous IVIG (n = 49)	Standard risk cytogenetics (n = 54)	2 or more total IRHs (n = 67)
On IVIG	0.81	0.48	0.65	1.04
Off IVIG	1.08	0.78	1.01	1.43

IgRT > 1 yr treated pts had improved survival



Daratumumab in combination with proteasome inhibitors, rapidly decreases polyclonal immunoglobulins and increases infection risk among relapsed multiple myeloma patients: a single center retrospective study

Roy Vitkon, Dan Netanely, Shai Levi, Tomer Ziv-Baran, Ronit Ben-Yzak, Ben-Zion Katz, Noam Benyamini, Svetlana Trestman, Moshe Mittelman, Yael Cohen and Irit Avivi



REGULAR ARTICLE

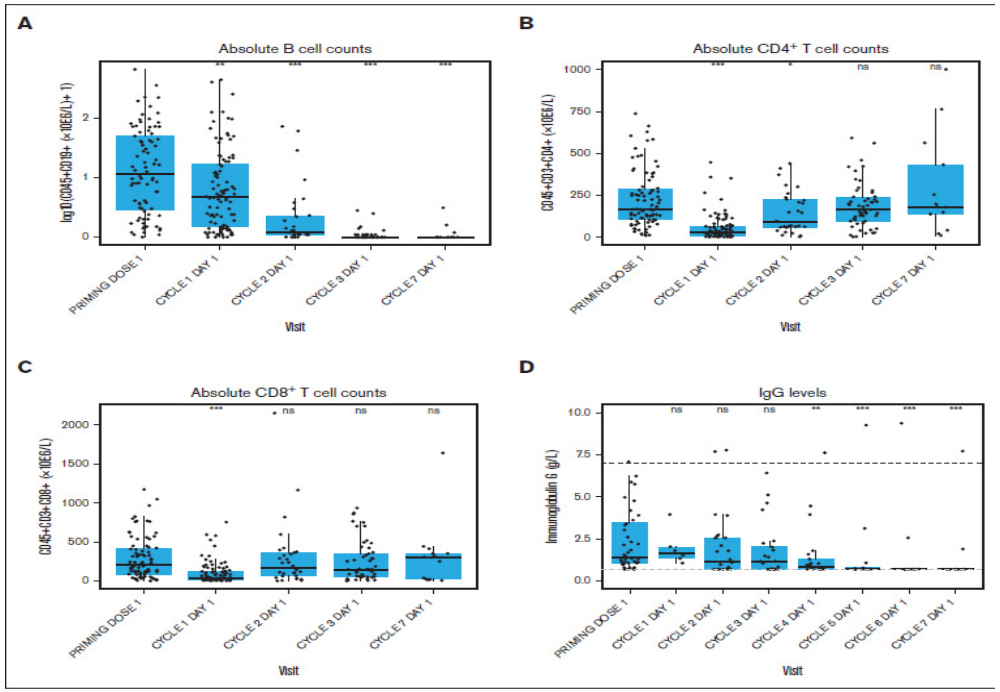
blood advances

Teclistamab impairs humoral immunity in patients with heavily pretreated myeloma: importance of immunoglobulin supplementation

Kristine A. Frerichs,[1,2] Christie P. M. Verkleij,[1,2] Maria Victoria Mateos,[3] Thomas G. Martin,[4] Cesar Rodriguez,[5] Ajay Nooka,[6] Arnob Banerjee,[7] Katherine Chastain,[7] Alfredo Perales-Puchalt,[7] Tara Stephenson,[7] Clarissa Uhlar,[7] Rachel Kobos,[7] Bronno van der Holt,[8,9] Sandy Kruyswijk,[1,2] Maria T. Kuipers,[1,2] Kaz Groen,[1,2] Deeksha Vishwamitra,[7] Sheri Skerget,[7] Diana Cortes-Selva,[7] Margaret Doyle,[10] Hans L. Zaaijer,[11] Sonja Zweegman,[1,2] Raluca I. Verona,[7] and Niels W. C. J. van de Donk[1,2]

Key Points

- Teclistamab induces severe defects in humoral immunity with decreased polyclonal immunoglobulin levels and impaired vaccination responses.
- IVIG use was associated with a significantly lower risk of serious infections among patients receiving teclistamab treatment.



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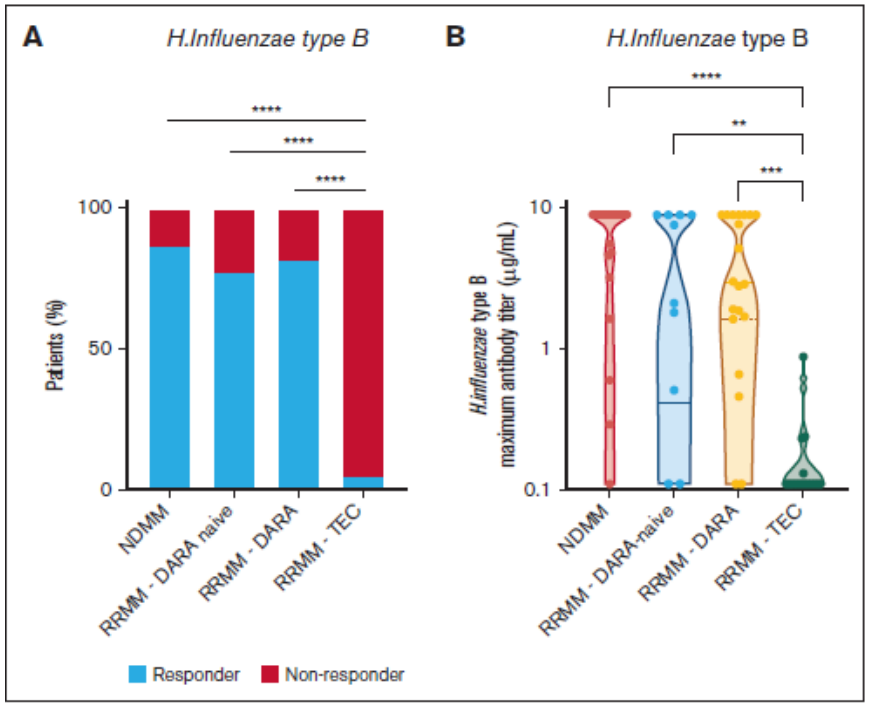

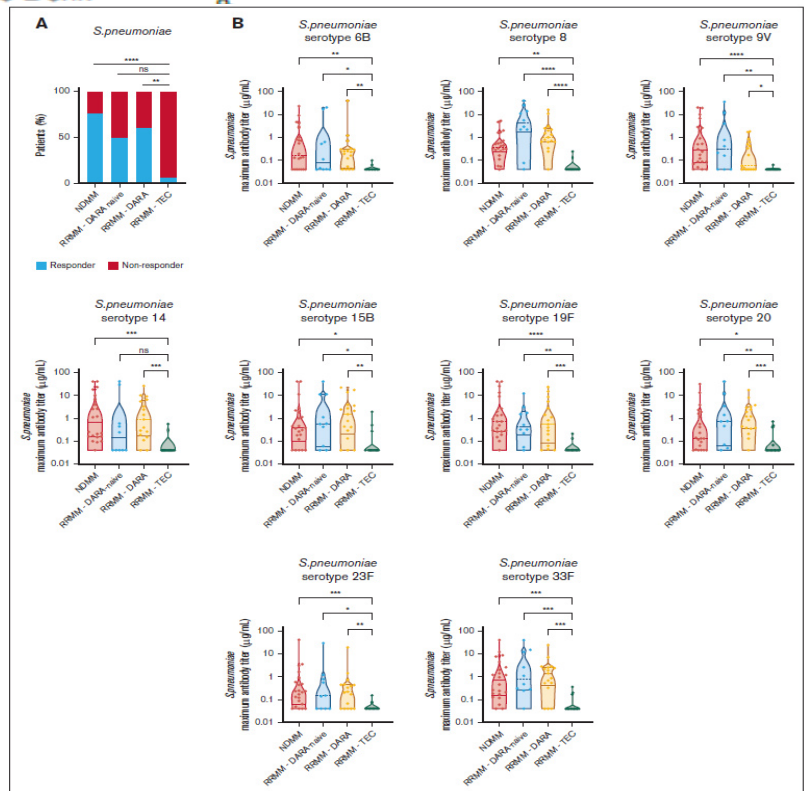

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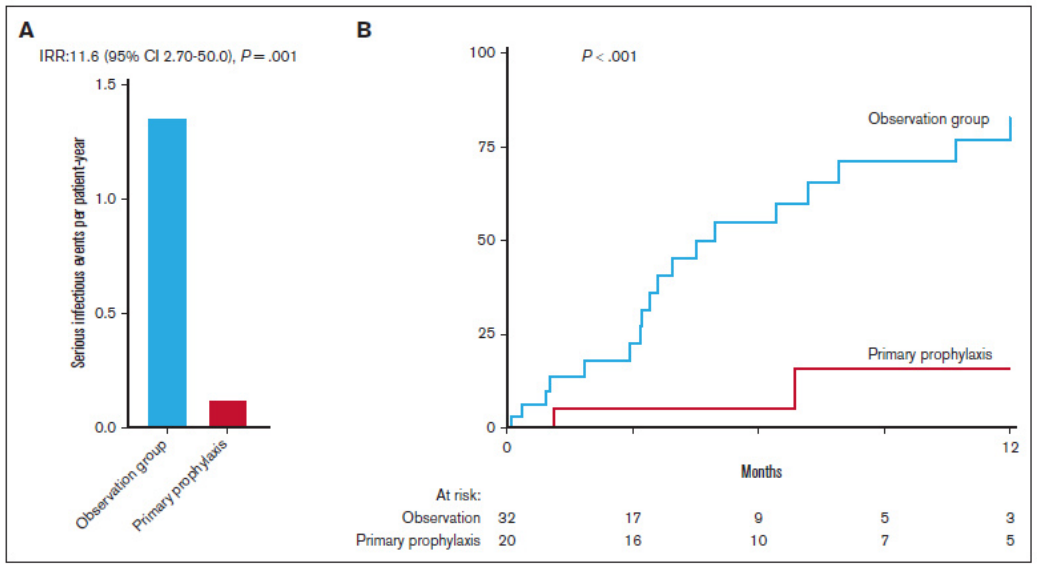


Figure 4. IVIG supplementation reduces the frequency of serious infections in patients treated with teclistamab. (A) Serious (grade ≥ 3) infectious events per patient-year in patients treated with teclistamab according to treatment with IVIG (primary prophylaxis) or without IVIG (observation group). (B) Cumulative incidence plot of time to first serious infection in patients treated with teclistamab according to treatment with IVIG (primary prophylaxis) or without IVIG (observation group). IRR, incidence rate ratio.

Table 2. Serious infections by type and pathogen according to treatment with and without IVIG

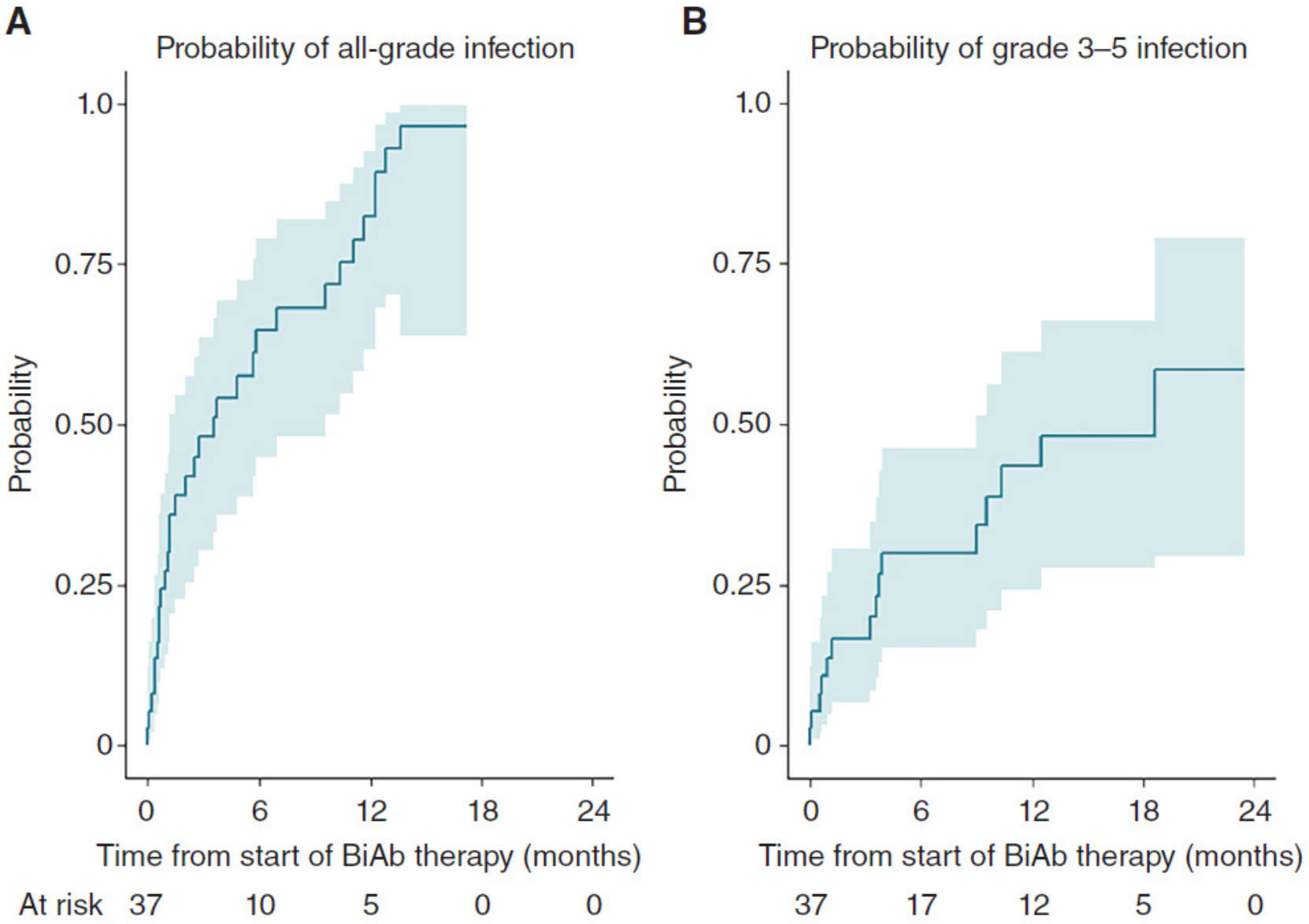
	IVIG as primary prophylaxis	No IVIG
Pneumonia/pneumosepsis	1 episode (also with breast abscess) • *P. aeruginosa* (n = 1)	11 episodes • *P. aeruginosa* (n = 5) • *P. aeruginosa* and *Klebsiella pneumoniae* (n = 1) • *Enterobacter cloacae* (n = 1) • Infuenza A + *P. aeruginosa* (n = 1) • *Moraxella catarrhalis* (n = 1) • No pathogen (n = 2)
Pneumonia and empyema	0	2 episodes • *P aeruginosa* (n = 1) • *Moraxella catarrhalis* (n = 1)
Urosepsis	1 episode • *E. coli* (n = 1)	3 episodes • *E. coli* (n = 2) • *Citrobacter freundii* (n = 1)
COVID-19	0	4 episodes

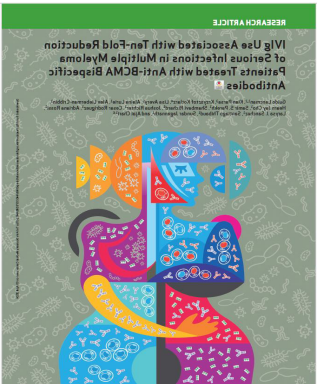
RESEARCH ARTICLE

IVIg Use Associated with Ten-Fold Reduction of Serious Infections in Multiple Myeloma Patients Treated with Anti-BCMA Bispecific Antibodies

Guido Lancman[1,2], Kian Parsa[3], Krzysztof Kotlarz[4], Lisa Avery[5], Alaina Lurie[1], Alex Lieberman-Cribbin[1], Hearn Jay Cho[1], Samir S. Parekh[1], Shambavi Richard[1], Joshua Richter[1], Cesar Rodriguez[1], Adriana Rossi[1], Larysa J. Sanchez[1], Santiago Thibaud[1], Sundar Jagannath[1], and Ajai Chari[1,6]


RESEARCH ARTICLE
IVIg Use Associated with Ten-Fold Reduction
of Serious Infections in Multiple Myeloma
Patients Treated with Anti-BCMA Bispecific
Antibodies


A
Probability of all-grade infection
Probability
1.0
0.75
0.50
0.25
0
0
6
12
18
24
Time from start of BiAb therapy (months)
At risk 37 10 5 0 0
B
Probability of grade 3–5 infection
Probability
1.0
0.75
0.50
0.25
0
0
6
12
18
24
Time from start of BiAb therapy (months)
37 17 12 5 0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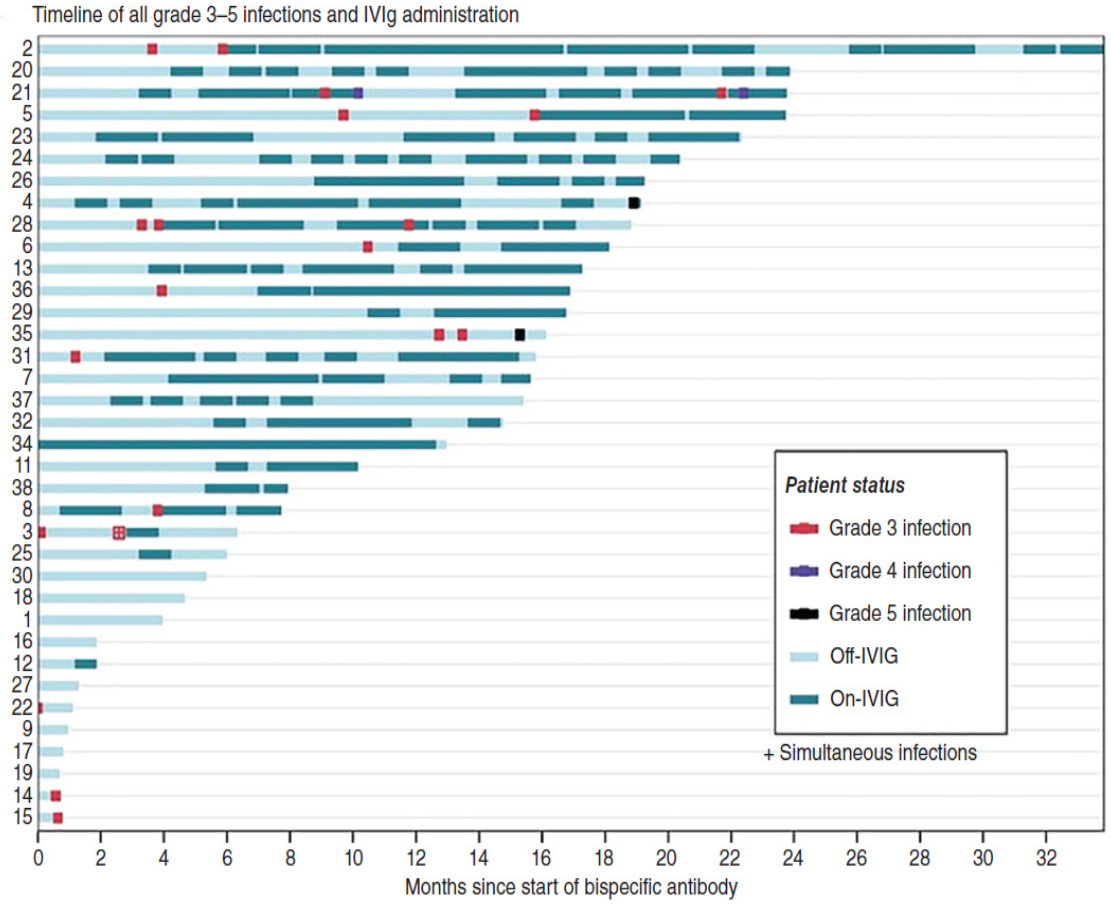
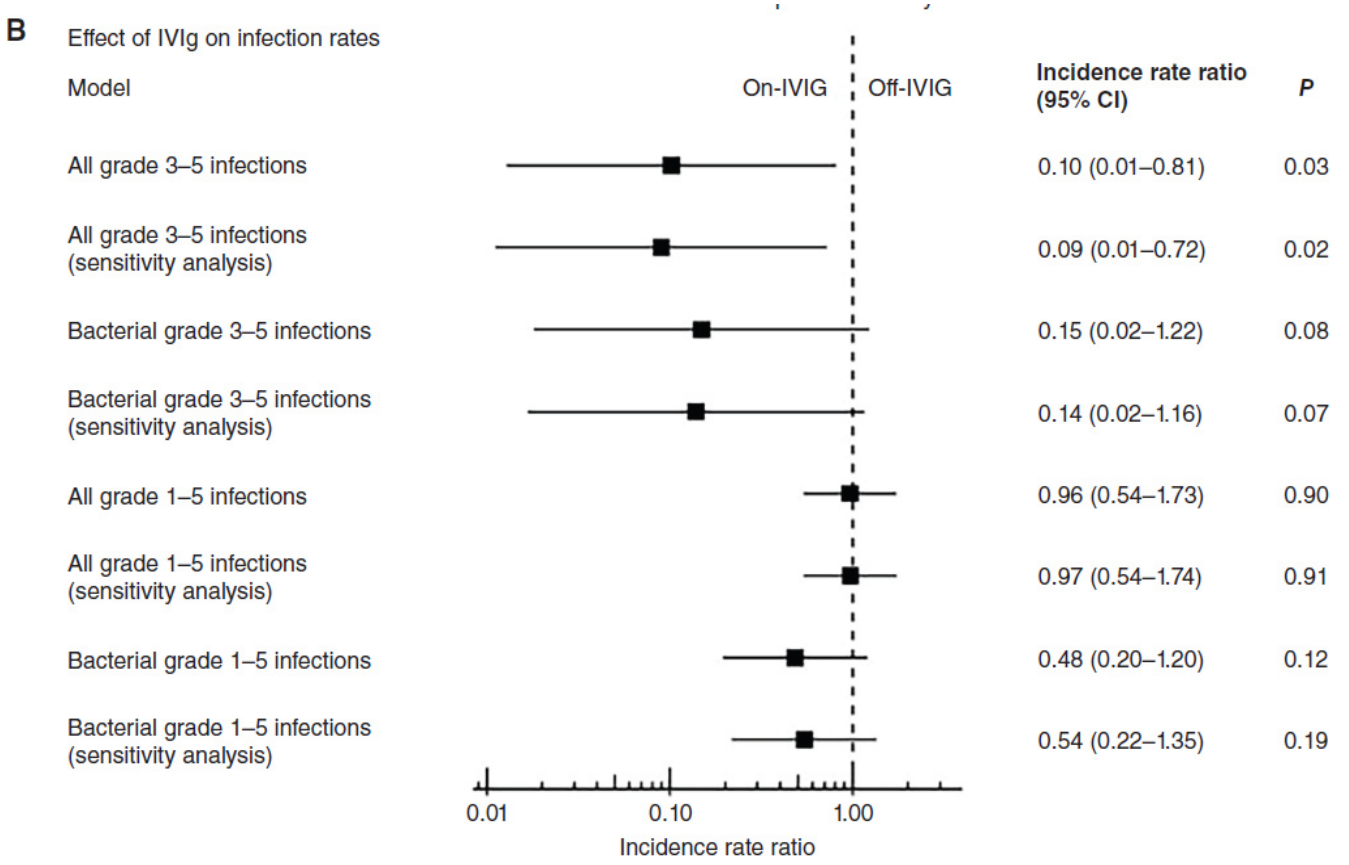

Timeline of all grade 3–5 infections and IVIg administration
2
20
21
5
23
24
26
4
28
6
13
36
29
35
31
7
37
32
34
11
38
8
3
25
30
18
1
16
12
27
22
9
17
19
14
15
Patient status
Grade 3 infection
Grade 4 infection
Grade 5 infection
Off-IVIG
On-IVIG
+ Simultaneous infections
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
Months since start of bispecific antibody


B
Effect of IVIg on infection rates
Model
On-IVIG
Off-IVIG
Incidence rate ratio (95% CI)
P
All grade 3–5 infections
0.10 (0.01–0.81)
0.03
All grade 3–5 infections (sensitivity analysis)
0.09 (0.01–0.72)
0.02
Bacterial grade 3–5 infections
0.15 (0.02–1.22)
0.08
Bacterial grade 3–5 infections (sensitivity analysis)
0.14 (0.02–1.16)
0.07
All grade 1–5 infections
0.96 (0.54–1.73)
0.90
All grade 1–5 infections (sensitivity analysis)
0.97 (0.54–1.74)
0.91
Bacterial grade 1–5 infections
0.48 (0.20–1.20)
0.12
Bacterial grade 1–5 infections (sensitivity analysis)
0.54 (0.22–1.35)
0.19
0.01
0.10
1.00
Incidence rate ratio

Blood Cancer Journal www.nature.com/

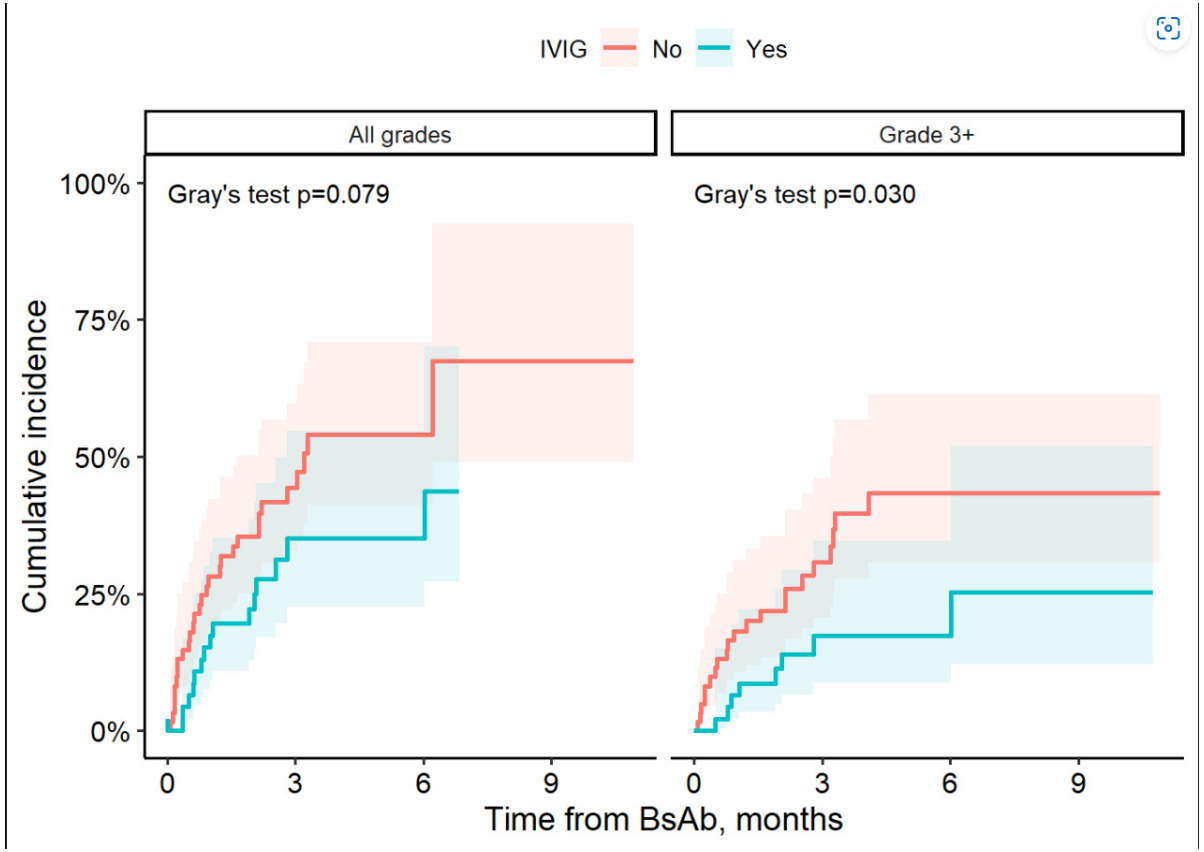
ARTICLE OPEN

Check for updat

Teclistamab in relapsed refractory multiple myeloma: multi-institutional real-world study

Meera Mohan[1,8], Jorge Monge[2,8], Nishi Shah[3,8], Danny Luan[2], Mark Forsberg[3], Vineel Bhatlapenumarthi[1], Metodi Balev[4], Anannya Patwari[1], Heloise Cheruvalath[5], Divaya Bhutani[4], Sharmilan Thanendrarajan[6], Binod Dhakal[1], Maurizio Zangari[6], Samer Al-Hadidi[6], Dennis Cooper[3], Suzanne Lentzsch[4], Frits van Rhee[7], Anita D'Souza[1], Aniko Szabo[7], Carolina Schinke[6,9] and Rajshekhar Chakraborty[4,9]✉

- recipients of IVIG had a statistically significant reduction in rates of all grades (0.95 vs 0.45; p = 0.005) and ≥ grade 3 infection (0.61 vs 0.24; p = 0.011) per 100 days
- "In the absence of prior or ongoing RCTs testing IVIG in the setting of BCMA bsAbs, the cumulative evidence strongly suggests a substantial benefit in terms of reducing infection risk"



Use of Immunoglobulin Replacement Therapy

- **For whom…?**
  - IgRT should be considered for infection prevention in any patient who experiences severe hypogammaglobulinemia **and** who has previously experienced a severe bacterial infection that could be considered related to MM diagnosis or treatment
  - Patients who experience recurrent or persistent infections over a 12-month period, despite appropriate anti-infective treatment
  - In patients who have serum IgG concentrations > 6 g/L, experience recurrent infections, and have a poor vaccine response, IgRT can be considered
- **How much…?** Dosing regimen:
  - IVIG: 0.2 to 0.4 g/Kg q3-4 weeks
  - SCIG: loading dose: 0.2 to 0.5 g/kg actual body weight ;
    maintenance: cumulative monthly dose of the order of 0.4 to 0.8 g/kg actual body weight

IgRT use with immunotherapy in MM-recommendations

IMWG- infections[1] : We suggest a targeted approach, limiting replacement therapy to patients with serum IgG concentrations that are less than 400 mg/dL and who have severe and recurrent infections by encapsulated bacteria (or other pathogens reasonably thought to be due to hypogammaglobulinaemia), despite appropriate antimicrobial prophylaxis and immunisation (NCCN level 2A). The subcutaneous and intramuscular formulations are as protective as the intravenous formulation

Consensus panel[2]:

- IgG levels <400 mg/dl (level IIC)
- Patients who have experienced ≥2 severe recurrent infections by encapsulated bacteria, regardless of IgG level (level IIC)
- Patients with a life-threatening infection (level III)
- Patients with documented bacterial infection with no or insufficient response to antibiotic therapy (level IIC)

[1]Raje et al. Lancet Haematol 2022; 9: 143–61. [2]Raje et al.Blood Cancer Journal (2023) 13:116

IgRT use with immunotherapy in MM-recommendations

COMMIT[1]: It is reasonable to recommend IVIG replacement every

4 weeks in recipients of BsAb starting the second month of therapy and continuing

until the end of therapy or until serum IgG levels reach >400 mg/dL, whichever is longer

IMWG- T cell engagers[2] the preventive role of IVIG remains unclear, with low quality evidence supporting its role. However, there is emerging data that IVIG can protect against serious (grade ≥3) infections. Thus consensus recommendation is that all patients with IgG less than 400 mg/dL receive replacement IVIG. IVIG should be considered in all patients with severe immunoparesis irrespective of the target

[1]Mohan et al. Br J Haematol. 2023;203:736–746. [2]Rodriguez-otero Lancet Oncol 2024; 25: e205–16

SC Immunoglobulin (SCIG) Replacement Therapy

- **No need for IV access**
- **Faster administration**
- **Self administration at the patient's home**

Contents lists available at ScienceDirect

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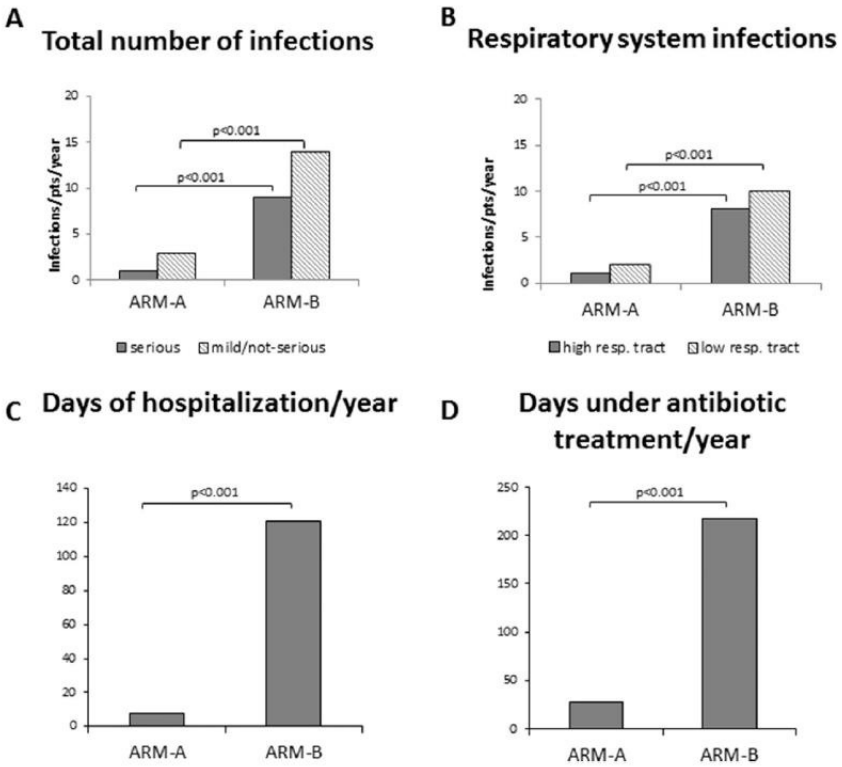
Angelo Vacca, Assunta Melaccio, Azzurra Sportelli, Antonio G. Solimando, Franco Dammacco, Roberto Ria *

Department of Biomedical Sciences and Human Oncology, Section of Internal Medicine and Clinical Oncology, University of Bari "Aldo Moro" Medical School, Bari, Italy

Table 2
Total number of infectious episodes during the study.

	Patients	
	Arm-A: SCIg	Arm-B: controls
Major infections		
Sepsis	–	24
Bacterial pneumonia	–	18
Bronchitis with sepsis	–	43
Pharyngo-tracheitis with sepsis	2	24
Acute sinusitis	–	5
Erysipelas	–	12
Urinary infection with sepsis	1	32
Fever of unknown origin	13	32
Minor infections		
Tracheobronchitis	32	64
Bacterial skin infection	11	16
Bacterial stomatitis	6	12
Lower urinary tract infection	19	36
Thoracic herpes zoster	1	15



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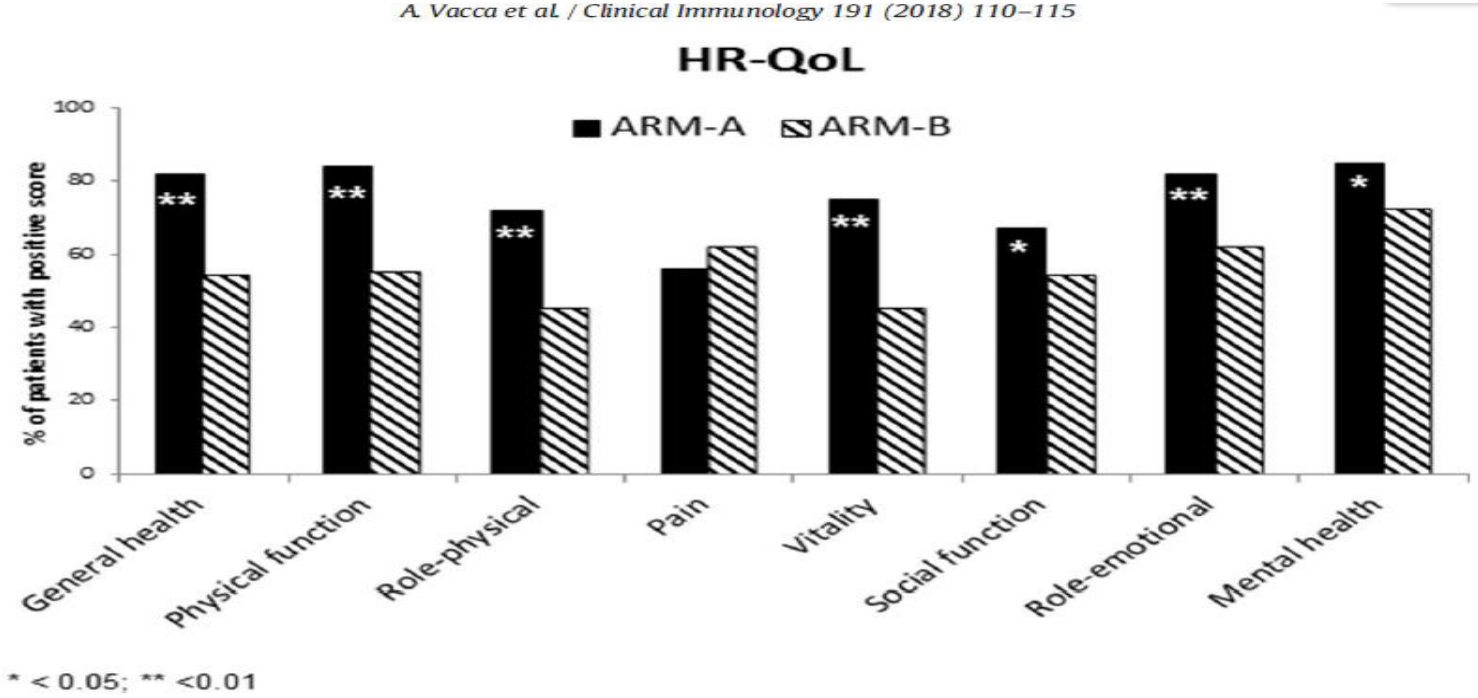

Fig. 4. Graphic report of patient survey for health-related quality of life (SF-36 questionnaire).

What is *f*SCIG (HyQvia) [1]

- *f*SCIG has 2 components:

Recombinant Human Hyaluronidase (rHuPH20)

- Enhances dispersion and absorption of Ig, allowing for greater volumes to be delivered in a SC infusion site

Immune Globulin Infusion (Human) **10%**

- Provides the therapeutic effect

Recombinant Human Hyaluronidase		Human Normal Immunoglobulin 10%	
Units	Volume (mL)	Protein (grams)	Volume (mL)
200	1.25	2.5	25
400	2.5	5	50
800	5	10	100
1,600	10	20	200
2,400	15	30	300

For example:
Adult : ~0.5g/kg/month
60kg = 30g/month = 300 ml
For PID indication.

SID 0.2–0.4 g/kg

HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase].
Ig=immunoglobulin; SC=subcutaneous.
1. HYQVIA Prescribing Information, 2020

IgRT monitoring recommendations

- IgRT should be evaluated regularly by assessing the patient's antibody recovery (increasing Ig concentrations and response to vaccines) as well as their clinical response
- It was recommended in the European expert consensus that IgRT should be discontinued in patients with HMs when infections are controlled for ≥6 months and show signs of immunological recovery, such as recovery of non- paraprotein IgG, IgA, or IgM concentrations
  - In patients in whom *infections are not optimally controlled*, we recommend that IgRT should be continued with consideration of an increased Ig dose
  - In patients with *reduced infection frequency and any evidence of immune function recovery*, we recommend that IgRT be discontinued when parameters are predictive of a safe withdrawal, this being based on clinical judgment and supportive laboratory parameters

חג שבועות!