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IMMUNE TOLERANCE INDUCTION IN THE ERA OF EMICIZUMAB – STILL THE FIRST CHOICE FOR PATIENTS WITH HAEMOPHILIA A AND INHIBITORS?

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SELECTED HIGHLIGHTS

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BACKGROUND

- The development of **inhibitors to factor VIII (FVIII) is a serious complication** of clotting factor replacement therapy associated with increased morbidity and mortality[1]
  - Inhibitors occur in around 1 in 3 previously untreated patients with severe haemophilia A (HA) and less than 1 in 4 patients with mild/moderate HA
- According to guidelines patients with inhibitors should have access to **immune tolerance induction (ITI) for eradication of inhibitors** and to suitable haemostatic agents at specialized centres[2]
  - Interventions can be limited by reimbursement and challenges to adherence
- The European Haemophilia Therapy Strategy Board conducted **surveys** on inhibitor management in Europe in **2004 and 2012**[3,4]
- The European Collaborative Haemophilia Network (ECHN) conducted a **follow-up survey in late 2020/early 2021** to determine:[1]
  - Whether ITI is still used in the routine management of patients with HA with inhibitors
  - Which ITI dosing regimens are currently used, and in which patients
  - Whether the availability of emicizumab has influenced ITI treatment decisions

1. Holstein K, et al. Haemophilia. 2021. DOI: 10.1111/hae.14470; 2. Srivastava A, et al. Haemophilia. 2020;26 Suppl 6:1-158;
3. Astermark J, et al. Haemophilia. 2006;12:363-71; 4. Holstein K, et al. Thromb Res. 2016;148:38-44

RESULTS:
DEMOGRAPHICS AND INHIBITORS INCIDENCE

- The survey was completed by ECHN members from **18 centres representing 17 countries** in the Europe/Middle East region between November 2020 and January 2021
- 18 respondents treated a **total of 4,955 patients** (3,723 adults and 1,232 children):
  - 2,055 (41.5%) with mild HA
  - 499 (10.1%) with moderate HA
  - 2,401 (48.5%) with severe HA
- **193 patients had inhibitors** at time of survey completion:
  - 22 (11.4%) with low-responding (LR) inhibitors: peak titre <5 Bethesda units (BU)/mL
  - 112 (58.0%) with high-responding (HR) inhibitors: peak titre 5–200 BU/mL
  - 59 (30.6%) with very high-responding (VHR) inhibitors: >200 BU/mL
- Majority (93.3%) of patients with current inhibitors had severe HA

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RESULTS:
ITI TREATMENT PATTERNS IN PATIENTS WITH A CURRENT INHIBITOR

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Patients with current inhibitors and ITI treatment performed

	All patients (n=193)	Mild/moderate HA (n=13)	Severe HA (n=180)
LR inhibitors, n	22	4	18
Received ITI	13	0	13
ITI failure	7	0	7
Ongoing ITI	6	0	6
HR inhibitors, n	112	9	103
Received ITI	61	3	58
ITI failure	46	3	43
Ongoing ITI	15	0	15
VHR inhibitors, n	59	0	59
Received ITI	42	0	42
ITI failure	31	0	31
Ongoing ITI	11	0	11

Data represents number of patients treated as reported by all respondents surveyed

ITI treatment in patients with ITI ongoing (all severe HA)

Dosing		LR[a]	HR[a]	VHR[b]
Less than daily	**Total, N**	**6**	**7**	**11**
	On emi, n (%)	1/6 (16.7)	6/7 (85.7)	4/11 (36.4)
	On BPA, n (%)	2/6 (33.3)	5/7 (71.4)	6/11 (54.6)
Daily up to 100 IU/kg/day	**Total, N**	**0**	**3**	**0**
	On emi, n (%)	-	0	-
	On BPA, n (%)	-	3/3 (100)	-
101–200 IU/kg/day	**Total, N**	**0**	**2**	**0**
	On emi, n (%)	-	0	-
	On BPA, n (%)	-	1/2 (50)	-
>200 IU/kg/day	**Total, N**	**0**	**0**	**0**

Respondents were able to select >1 response; data is missing for 3 patients
No patients with mild/moderate haemophilia were treated with ongoing ITI
[a] Data as reported by 14 respondents; [b] Data as reported by 17 respondents

BPA, bypassing agent prophylaxis; emi, emicizumab prophylaxis; HA, haemophilia A; HR, high responding; ITI, immune tolerance induction; IU, international units; LR, low responding; VHR, very high responding

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RESULTS:

TREATMENT PATTERNS OF PATIENTS WHO DEVELOPED NEW INHIBITORS SINCE FEBRUARY 2018 AND SUCCESS RATES OF ITI

	Mild/moderate HA (n=6)		Severe HA (n=17)	
	LR	**HR/VHR**	**LR**	**HR/VHR**
Total, N[a] Age 0–3 years Age 4–18 years Age 19–60 years Age >60 years	3 0 0 2 1	3 0 2 0 1	5 4 1 0 0	12 9 2 1 0
Patients started on ITI overall, n/N (%)	1/3 (33.3)[b]	3/3 (100)	3/5 (60)	8/12 (66.7)
Started ITI immediately	0	2/3 (66.7)	3/5 (60)	7/12 (58.3)
Patients started on ITI + emi, n/N (%)	0	3/3 (100)	2/5 (40)	3/12 (25)
Started emi before ITI	0	0	0	1/12 (8.3)
Started emi at start of ITI	0	0	1/5 (20)	0
Started emi during ITI due to bleeds	0	3/3 (100)	1/5 (20)	1/12 (8.3)
Patients started on emi only, n/N (%)	1	0	1/5 (20)[c]	4/12 (33.3)[d]

[a] Data represents number of patients treated as reported by 15 respondents overall
[b] ITI was stopped and the treatment was switched to emi due to patient/caregiver preference
[c] Reasons for emi prophylaxis only: physician, patient, and caregiver preference
[d] Reasons for emi prophylaxis only: wait for better venous access in accordance with patient/caregiver preference; two preferred emicizumab over ITI, two chose this approach because of expected low probability of ITI success

emi, emicizumab prophylaxis; HR, high responding; ITI, immune tolerance induction; LR, low responding; VHR, very high responding

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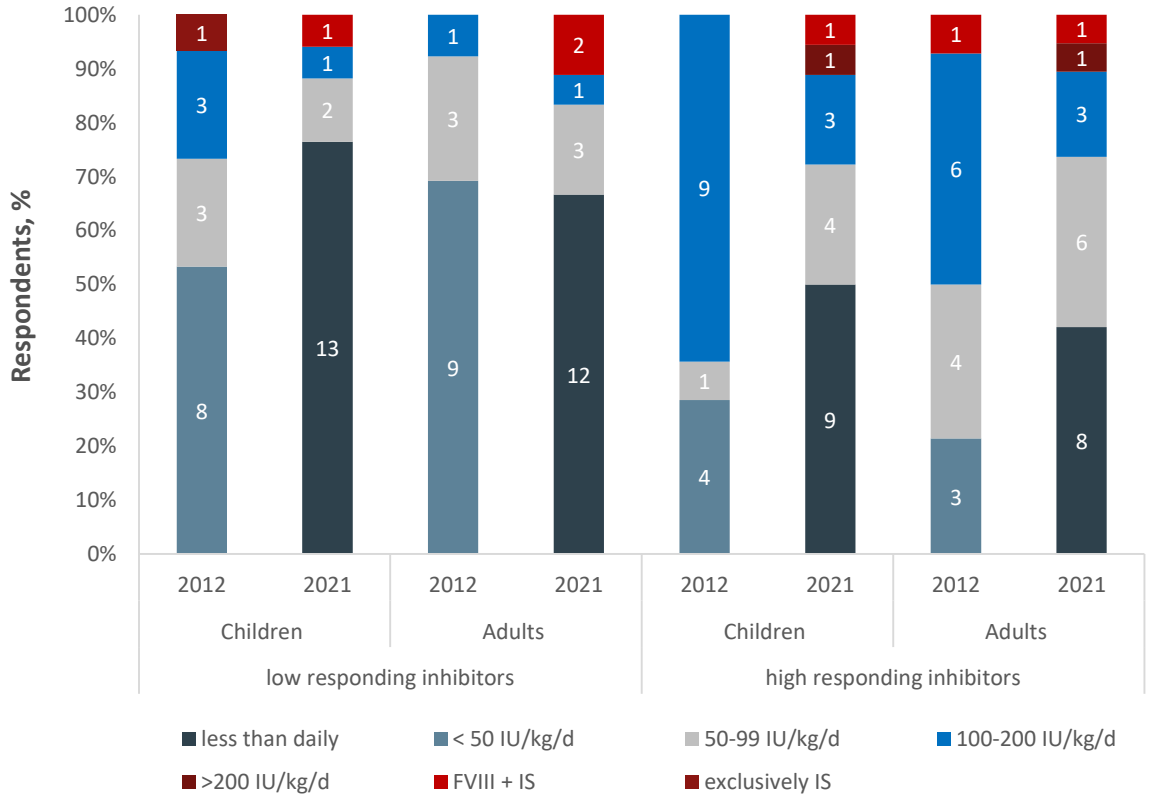
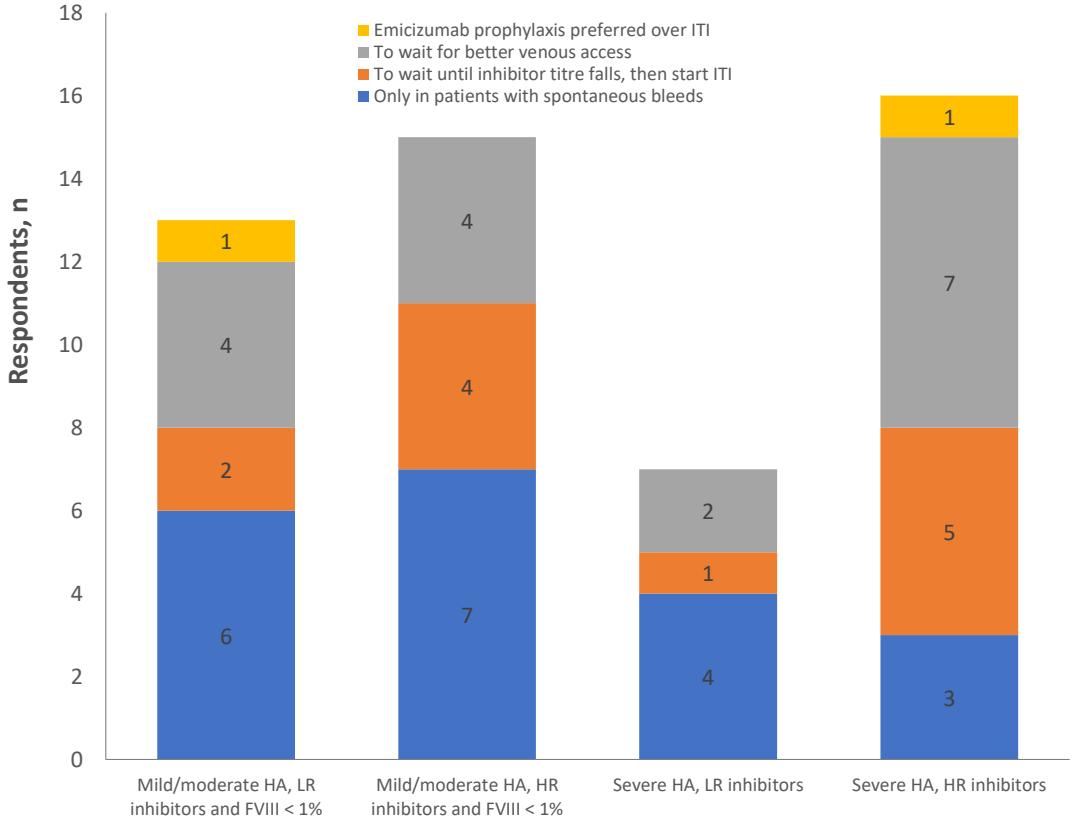
RESULTS:
APPROACH TO A NEW PATIENT WITH INHIBITORS

Preferred dosing regimen in a potential new patient with severe HA with inhibitors (2012 vs 2021)



Reasons for starting emicizumab prophylaxis without ITI[a]



[a] Figure represents responses from a total of 17 respondents overall; respondents were able to select more than one response

d, day; FVIII, factor VIII; HA, haemophilia A; HR, high responding; ITI, immune tolerance induction; IU, international units; IS, immunosuppression; LR, low responding

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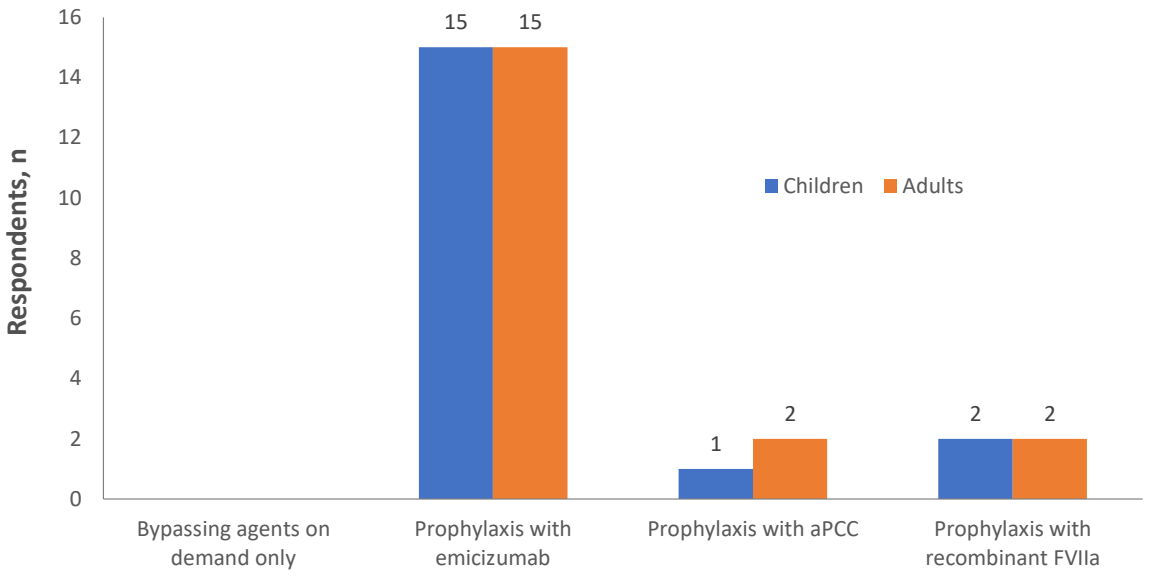
RESULTS:
APPROACH TO A PATIENT WITH INHIBITORS

- The treatment approach to **children and adults** with new inhibitors was **similar**
- In the **first line**, around two-thirds of respondents would prefer **the current product** over a VWF-containing product
- In **adults with long-standing inhibitors**, more than two-thirds of respondents would prefer a **VWF-containing product**
- 40% of respondents would use a **central line** for ITI
- Half of respondents reported a **maximum duration of ITI** (12–36 months); the other half did not limit ITI duration
- All respondents indicated that they would give **prophylaxis during ITI**, with initiation guided by bleeding patterns
  - More than three-quarters (77%) would use emicizumab prophylaxis

Treatment of patients failing first ITI[a]



[a] Data represents number of respondents from a total of 16 respondents overall. Respondents were able to indicate more than one response
aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; ITI, immune tolerance induction; VWF, von Willebrand factor
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DISCUSSION

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Comparison with the 2016 survey

- A **greater proportion** of patients with current inhibitors were **treated with ITI**: 60% from 2018–2021 vs ~45% from 2002–2012
- A **trend towards lower ITI dosing** was observed:
  - Less than daily dosing was used in 83% of ongoing ITI and 69% of ITIs performed overall from 2018–2021
  - A regimen of <50 IU/kg/day was used in 11.5% of ongoing ITI and 31% of ITIs performed overall from 2002–2012

This is the largest study of its kind to date, and the first since emicizumab was approved in 2018

- All respondents indicated that they would initiate prophylaxis during ITI; results show a strong **preference for emicizumab in this setting** when available and reimbursed
- In patients **failing a first ITI attempt**, there is increasing acceptance of **emicizumab prophylaxis**

Unmet needs

- Consensus on the **first-line standard of care**
- An **approach to ITI failure** in patients with VHR inhibitors
- Impact of **cost and availability** use of novel products
- ITI in **mild/moderate HA**

HA, haemophilia A; ITI, immune tolerance induction; IU, international units; VHR, very high responding

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CONCLUSIONS

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ITI remains a mainstay for haemophilia treatment

Emicizumab prophylaxis has become a preferred first-line approach to protect against bleeds and represents an alternative to burdensome ITI in certain patient groups

Prospective clinical trials on the concomitant use of ITI and emicizumab prophylaxis will be helpful for the development of new ITI protocols for patients with inhibitors

ITI, immune tolerance induction

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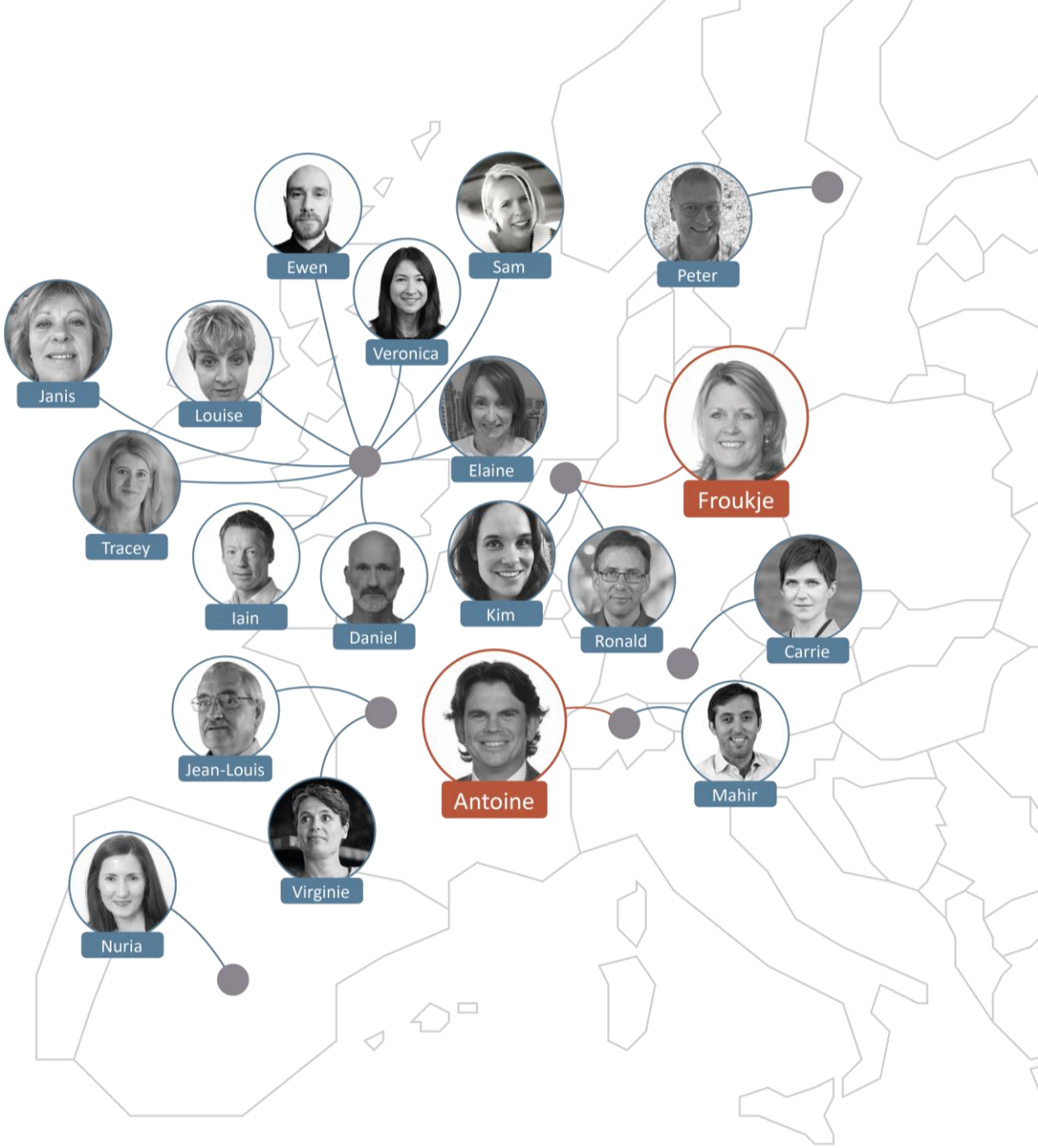

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