

Immune tolerance induction in the era of emicizumab – still the first choice for patients with haemophilia A and inhibitors?

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Abstract

Introduction: The development of inhibitory antibodies is a severe complication of clotting factor replacement therapy in patients with severe haemophilia A (HA). Current World Federation of Hemophilia (WFH) guidelines for haemophilia care indicate that eradication of inhibitors is best achieved through immune tolerance induction (ITI) therapy.

Aim: The European Collaborative Haemophilia Network conducted a survey to determine whether ITI is still used in the routine management of patients with HA, and whether the availability of emicizumab prophylaxis has influenced treatment decisions.

Methods: The survey was conducted in late 2020/early 2021 in 18 centres representing 17 countries in the Europe/Middle East region treating a total of 4955 patients, and included sections specific to patient and centre demographics, treatment protocols (both ITI and prophylactic), inhibitor development and initiation of ITI, treatment success, and the incidence of adverse events.

Results: While our results indicate that ITI can still be considered a mainstay of treatment for patients with HA with inhibitors, less than daily dosing of ITI in combination with emicizumab prophylaxis is becoming commonplace across the spectrum of disease severity, with initiation being guided by bleeding patterns. The most frequently cited reasons for not initiating emicizumab prophylaxis were availability or reimbursement issues.

Conclusion: ITI remains a mainstay for haemophilia treatment of patients with HA with inhibitors, but emicizumab has become a preferred first-line approach to protect against bleeds and represents an alternative to burdensome ITI in certain patient groups.

KEYWORDS

emicizumab, factor VIII, haemophilia A, immune tolerance induction, inhibitors, prophylaxis

1 | INTRODUCTION

The development of inhibitory antibodies to factor VIII (FVIII) is a serious complication of clotting factor replacement therapy occurring in around one-third of previously untreated patients with severe haemophilia A (HA). Inhibitor development usually occurs at a young age and is commonly associated with intensive clotting factor treatment.^{1–4} Inhibitors generally occur in less than one in four patients with mild/moderate HA, usually arising in adulthood and often being associated with certain genotypes.^{5,6}

Inhibitors are associated with a significant increase in morbidity and mortality.^{7–10} Therefore, the World Federation of Hemophilia (WFH) guidelines and European Principles of Haemophilia Care indicate that patients with inhibitors should have access to immune tolerance induction (ITI) for eradication of inhibitors, and to suitable haemostatic agents for control of bleeding, at specialized centres.^{11–13} Bypassing agents (BPA) and other suitable products should be available for patients who do not respond to enhanced factor dosages or ITI.^{11,13–15} However, many of these potential interventions can be limited by regional reimbursement. Furthermore, high-intensity ITI treatment regimens requiring rigorous adherence can be challenging for both patient and caregiver; non-adherence can reduce therapy success rates.¹⁰

In 2004 and 2012, the European Haemophilia Therapy Strategy Board (EHTSB) conducted surveys on inhibitor management in Europe.^{16,17} In late 2020/early 2021, the European Collaborative Haemophilia Network (ECHN) conducted a follow-up survey to determine whether ITI is still used in the management of patients with HA with inhibitors, which dosing regimens are used, and whether the availability of emicizumab has influenced these treatment decisions.

2 | MATERIALS AND METHODS

The survey was designed by ECHN working group members, and included sections specific to patient and centre demographics, inhibitor development and initiation of ITI, treatment protocols (both ITI and prophylactic), treatment success, and the incidence of adverse events as reported by each centre (Supplemental material). Surveys were sent by email to ECHN members; each named recipient was responsible for completion of the survey based on data from haemophilia treatment centres in their respective country, with data-collection assistance provided by centres as required. Patients were categorized by severity of HA, and as having either low responding (LR; peak titre < 5 BU [Bethesda units]/mL) or high responding/very high responding inhibitors (HR/VHR; peak titre 5–200 BU/mL and > 200 BU/mL, respectively) [11, 16–19]. ITI success was defined as normal half-life ($T_{1/2}$) for FVIII (> 6 hours), normal recovery of FVIII (> 66%), and no measurable inhibitor titre (cut-off > 0.5 BU).

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. Meetings were held by the working group members to collate and analyse survey data.

3 | RESULTS

This survey represents the treatment experience and protocols of 18 respondents treating a total of 4955 patients with mild ($n = 2055$), moderate ($n = 499$), or severe HA ($n = 2401$) across 17 countries: 1232 children (of whom 164 were age 0–3 years) and 3723 adults (of whom 770 were age > 60 years).

At time of survey completion (January 2021), 193 patients with current inhibitors were reported; 22/193 (11.4%) with LR, 112/193 (58.0%) with HR and 59/193 (30.6%) with VHR inhibitors. Most patients with current inhibitors had severe HA (180/193; 93.3%).

3.1 | ITI treatment patterns in patients with a current inhibitor

At the time of survey completion, a total of 116/193 patients (60.0%) had been treated with ITI (either a current ongoing treatment ['Ongoing ITI'] or as part of an earlier unsuccessful treatment regimen ['ITI failure']) across all centres surveyed (Table 1).

3.1.1 | Patients with severe HA

Of the 180 patients with severe HA and current inhibitors of any titre, 81 (45.0%) were previous ITI failures; 73/81 ITI failures (90.1%) were on emicizumab prophylaxis. Sixty-seven of the 180 patients (37.2%) had not received ITI at any time; 59/67 (88.1%) were on emicizumab prophylaxis. Reported reasons for not initiating ITI included problems with venous access (14/67 [20.1%]), preference for emicizumab prophylaxis (11/67 [16.4%]), patient or caregiver preference (15/67 [22.4%]), and low expected probability for success (15/67 [22.4%]).

ITI was ongoing in 32/180 (17.8%) patients with severe HA; 11/32 (34.4%) were on emicizumab prophylaxis and 17 (53.1%) on BPA prophylaxis. In patients on emicizumab prophylaxis, an ITI protocol with less than daily dosing was most commonly used, independent of inhibitor titre (Table 2). Of patients with ongoing ITI, 3/6 (50%) patients with LR inhibitors (two in the first line), 8/15 (53.4%) patients with HR inhibitors (four in the first line), and 6/11 (54.5%) with VHR inhibitors (three in the first line) were treated with a VWF-containing product.

3.1.2 | Patients with mild/moderate HA

Thirteen patients with mild/moderate HA and current inhibitors were reported: 4/13 (30.8%) and 9/13 (69.2%) had LR and HR inhibitors, respectively; none had VHR inhibitors. None of the patients with LR inhibitors were ever treated with ITI; one was on emicizumab due to patient/caregiver preference. Of the patients with HR inhibitors, 3/9 (33.3%) underwent ITI without success, two of whom were on emicizumab prophylaxis; 6/9 (66.7%) had never received ITI (three of whom were on emicizumab prophylaxis). No patient with mild/moderate HA with inhibitors was treated with ongoing ITI at

TABLE 1 Patients with current inhibitors and ITI treatment performed at study end, stratified by peak titre and severity

	All patients (n = 193)	Mild/moderate HA (n = 13)	Severe HA (n = 180)
LR inhibitors (peak titre < 5 BU/mL), n	22	4	18
Received ITI	13	0	13
ITI failure	7	0	7
Ongoing ITI	6	0	6
HR inhibitors (peak titre 5–200 BU/mL), n	112	9	103
Received ITI	61	3	58
ITI failure	46	3	43
Ongoing ITI	15	0	15
VHR inhibitors (peak titre > 200 BU/mL), 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.

BU, Bethesda units; HA, haemophilia A; HR, high responding; ITI, immune tolerance induction; LR, low responding; VHR, very high responding.

TABLE 2 ITI treatment in patients with ITI ongoing

n/N (%)		Severe HA		
Dosing		LR [†]	HR [†]	VHR [‡]
Less than daily	Total, N	6	7	11
	On emi	1/6 (16.7)	6/7 (85.7)	4/11 (36.4)
	On BPA	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	–	0	–
	On BPA	–	3/3 (100)	–
101–200 IU/kg/day	Total, N	0	2	0
	On emi	–	0	–
	On BPA	–	1/2(50)	–
> 200 IU/kg/day	Total, N	0	0	0

Respondents were able to select more than one response.

Data is missing for three patients.

No patients with mild/moderate haemophilia were treated with ongoing ITI. BPA, bypassing agent prophylaxis; emi, emicizumab prophylaxis; HA, haemophilia A; HR, high responding; IU, international units; LR, low responding; VHR, very high responding.

[†]Data as reported by 14 respondents.

[‡]Data as reported by 17 respondents.

the time of study completion. Reported reasons for not initiating ITI were preference for emicizumab prophylaxis (2/10 [20.0%] and patient/caregiver preference (5/10 [50.0%]).

3.2 | Treatment patterns of patients who developed new inhibitors since February 2018 and success rates of ITI

We aimed to explore the treatment decisions, dosing regimens, and success rates in patients who developed inhibitors since emicizumab

entered the market in February 2018. At time of survey completion, 23 patients were reported to have developed new inhibitors in the last 3 years; 17/23 (73.9%) had severe HA, 6/23 (26.1%) mild/moderate HA. Patient demographics and treatment patterns for patients who developed new inhibitors are shown in Table 3.

3.3 | Treatment and success rates of patients who developed new inhibitors

Median time to response was reported for 8 patients across all disease severity groups (all on less than daily dosing) and ranged from 4 to 20 months.

3.3.1 | Patients with severe HA who developed new inhibitors

For severe HA, the highest rate of ITI 'success' was reported in the patients who developed LR inhibitors: 5/5 (100%) achieved ITI success (three of whom were treated with less than daily dosing). Three of eight (37.5%) with HR inhibitors were categorized as a 'success', 3/8 (37.5%) as 'partial response' (two at less than daily dosing), and 2/8 (25%) as treatment failures. There were no treatment successes reported in patients with VHR inhibitors, but one partial response. Across all inhibitor titres, 11/16 (68.8%) patients were treated with less than daily dosing.

3.3.2 | Patients with mild/moderate HA who developed new inhibitors

One patient with mild/moderate HA and HR inhibitors was reported as a treatment success, and one as a partial success (both at less than

**TABLE 3** Patients who developed an inhibitor 2018–2021 and initiated ITI

	Mild/moderate HA (n = 6)		Severe HA (n = 17)	
	LR	HR/VHR	LR	HR/VHR
Total, N [†]	3	3	5	12
Age 0–3 years	0	0	4	9
Age 4–18 years	0	2	1	2
Age 19–60 years	2	0	0	1
Age > 60 years	1	1	0	0
Patients started on ITI overall, n/N (%)	1/3 (33.3) [‡]	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 ^b	0	1/5 (20) [§]	4/12 (33.3) [¶]

Emi, emicizumab prophylaxis; HR, high responding; LR, low responding.

[†]Data represents number of patients treated as reported by 15 respondents overall.

[‡]ITI was stopped and the treatment was switched to emicizumab prophylaxis due to patient/caregiver preference.

[§]Reasons for emi prophylaxis only: physician, patient, and caregiver preference.

[¶]Reasons for emi prophylaxis only: was to wait for better venous access in accordance with patient/caregiver preference, but two additionally preferred emicizumab over ITI, and two chose this approach because of expected low probability of ITI success.

daily dosing). There was a single reported patient with mild/moderate HA and VHR inhibitors categorized as a treatment success at less than daily dosing.

3.4 | Adverse events

One adverse event was reported in the overall population of patients with inhibitors during the study period: an allergic response following treatment with FVIII (both recombinant and plasma-derived). The patient was switched to emicizumab.

3.5 | Approach to a new patient with severe HA with inhibitors

Preferred ITI doses in comparison to the previous survey¹⁷ are displayed in Figure 1. A trend towards lower ITI dosing vs the previous survey was observed.

Emicizumab prophylaxis would be added in children and adults by 11/13 (84.6%) and 9/12 (75%) respondents choosing less than daily dosing, 2/2 (100%) and 2/3 (66.7%) respondents for daily up to 100 IU/kg, and 0/1 and 0/1 respondents for 100–200 IU/kg, respectively. All but one respondent would use FVIII without immunomodulation; none of the respondents would use immunomodulation exclusively.

3.6 | Approach to a new patient with mild/moderate HA with inhibitors

Seven of 17 (41.2%) respondents indicated they would start ITI immediately in a patient with mild/moderate HA with HR inhibitors (FVIII < 1%). Ten (58.8%) respondents would not start ITI immediately, and two (11.8%) indicated that they would wait for the titre to decline to 10 BU before initiating ITI (max. 5–6 months). Twelve respondents (two who would initiate ITI immediately and 10 who would not) indicated that they would start emicizumab prophylaxis before attempting ITI in this patient group, for various reasons (Figure 2).

Just 2/17 (11.8%) respondents indicated that they would start ITI immediately in patients with mild/moderate HA with LR inhibitors: one at a dose of 25 IU/kg three times per week, one at 50 IU/kg every other day. Fifteen of 17 (88.2%) respondents would not start ITI immediately, 11/15 (73.3%) would continue FVIII prophylaxis and wait for spontaneous remission (max. 12 months [range 1–12 months]), and 10/15 (66.7%) would start emicizumab in this patient group (three indicated multiple reasons for this [Figure 2]; one indicated a preference for emicizumab prophylaxis alone over ITI).

3.7 | Product type for first-line treatment

The first-line treatment approach to new inhibitors was similar in children and adults: around two-thirds of respondents would prefer their current product (i.e. the last product used or the product used

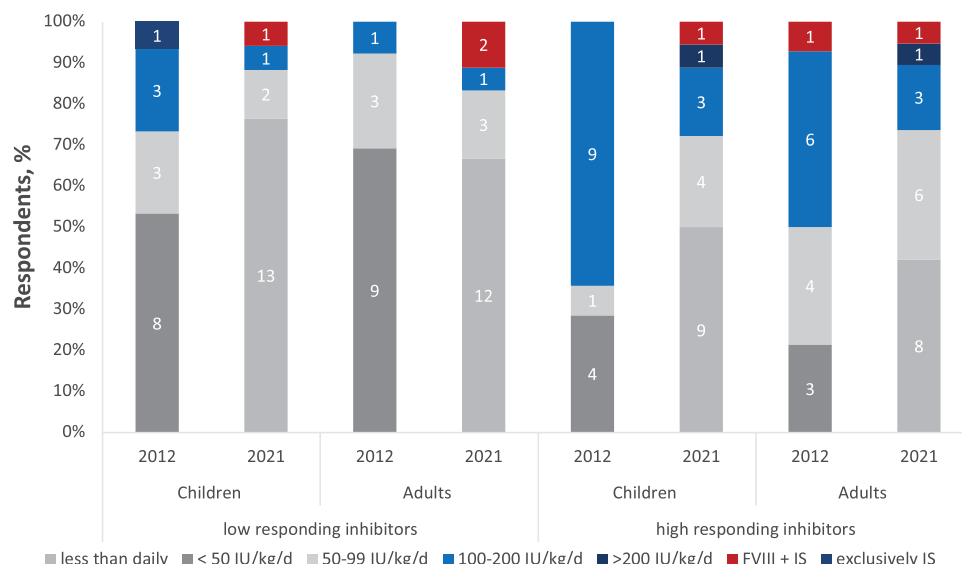


FIGURE 1 Preferred dosing regimen in a potential new patient with inhibitors (2012 vs 2021). d, day; FVIII, factor VIII; IU, international units; IS, immunosuppression

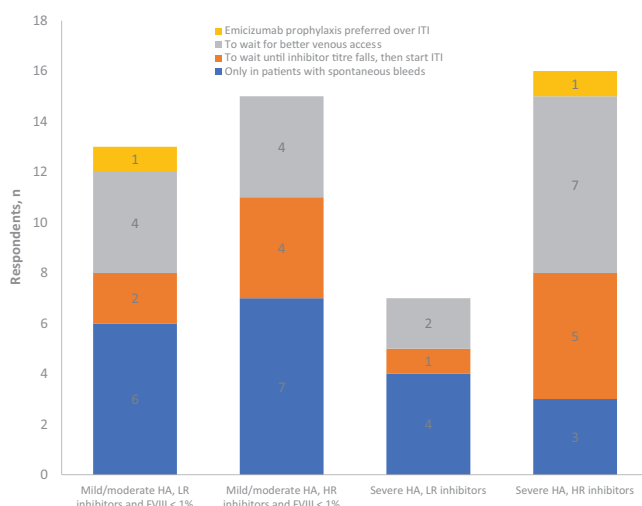


FIGURE 2 Reasons for starting emicizumab prophylaxis without ITI in a new patient with mild/moderate or severe HA with inhibitors. Data represents number of respondents from a total of 17 respondents overall. Respondents were able to select more than one response. FVIII, factor VIII; HA, haemophilia A; HR, high responding; ITI, immune tolerance induction; LR, low responding

at inhibitor detection) over a VWF-containing product. In adults with long-standing inhibitors, more than two-thirds of respondents (11/16; 68.8%) would prefer a VWF-containing product, with just three and one respondent choosing current or recombinant products, respectively. Six of 15 (40%) respondents would use a central line for ITI, but many respondents expressed concerns with this approach, with a decision to take this approach being influenced by venous access and patient age.

3.8 | Measuring ITI success

The previous survey defined ITI success as a normal half-life for FVIII (> 6 hours), normal recovery of FVIII (> 66%), and no measurable inhibitor titre (cut-off > 0.5 BU)¹⁷; in mild/moderate haemophilia recovery of former basal FVIII level would also be required, but it was not quoted whether a re-challenge to FVIII would be mandatory.¹⁷ This was unchanged in the current survey, with respondents indicating that these criteria of success were of almost equal value. Eight of 16 (50%) respondents reported maximum duration of ITI of 12–36 months, the remaining eight respondents did not limit the duration of treatment.

3.9 | Prophylaxis during ITI

All 17 respondents would give prophylaxis during ITI, with initiation guided by bleeding patterns, including frequency, intensity, and the 'acceptable' number of bleeds in individual patients. Thirteen respondents (76.5%) indicated they would preferentially use emicizumab prophylaxis; nine respondents (52.9%) indicated that they would also consider prophylaxis with a bypassing agent (five with an activated prothrombin complex concentrate, and four with recombinant factor VIIa).

Emicizumab availability was limited in three centres; one respondent indicated emicizumab was not approved in their country. In each of these centres, respondents indicated that prophylaxis with a bypassing agent was a consideration, but responses suggest that this decision is guided by availability and individual patient need rather than a clear preference.

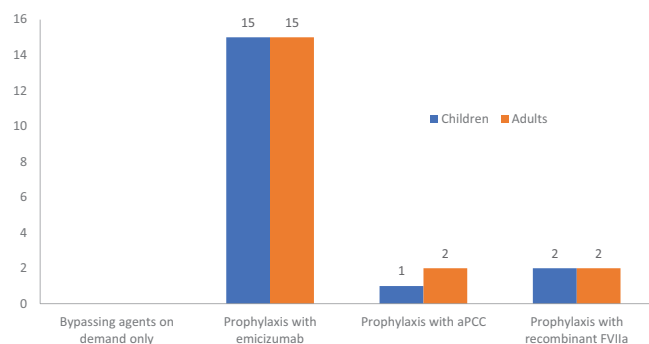


FIGURE 3 Treatment of patients failing first ITI. Data represents number of respondents from a total of 16 respondents overall. Respondents were able to indicate more than one response. aPCC, activated prothrombin complex concentrates; FVIII, factor VIII; ITI, immune tolerance induction

3.10 | Treatment of patients failing first ITI with high-dose factor using the current product

Eleven of 15 respondents (73.3%) indicated they would attempt ITI again in patients failing first ITI with a high-dose regimen, but using an alternative product, adding immunomodulation, and/or changing dose/regimen. While almost two-thirds of respondents (8/13 [61.5%]) indicated they would treat adults and children in the same way, survey responses indicate a general concern towards venous access in younger patients that might influence decisions to re-attempt ITI in this patient group. This decision is strictly related to the condition of the patient. There was strong preference for the use of emicizumab prophylaxis in both adults and children failing first high-dose ITI with the current product (Figure 3). All but one of 16 (93.8%) respondents would recommend emicizumab prophylaxis in this patient group.

4 | DISCUSSION

This survey was conducted across 18 haemophilia comprehensive care centres in the Europe/Middle East region to gather information on treatment approaches for patients with inhibitors across the haemophilia severity spectrum, with a particular focus on the use of bleeding prophylaxis alongside different ITI protocols. This is the largest study of its kind to date, and the first since emicizumab was approved in 2018. While direct comparison of the current survey data with earlier EHTSB surveys^{16,17} is limited due to low patient numbers and slightly different approaches, clear trends in treatment patterns can be traced.

In the current survey, 60% of patients with current inhibitors had been treated with ITI overall (62.8% in severe HA; 23.1% in mild/moderate HA), compared to ~45% in the 2016 survey (which included 11/133 patients with haemophilia B). A trend towards lower ITI dosing was observed, with less than daily dosing being used in 82.8% of ongoing ITI and 68.8% of ITIs performed 2018–2021, whereas in the previous survey only in 11.5% of ongoing ITI and 30.8% of ITIs per-

formed 2002–2012 a regimen with < 50 IU/kg/day was used.¹⁷ The trend to lower dosing is also reflected in the treatment choice for a potential new patient with inhibitors (Figure 1).

In the current survey, all patients with severe HA and LR inhibitors achieved ITI success; 3/8 (37.5%) with HR inhibitors were categorized as a treatment 'success'. In the 2016 survey, success rates in these groups were 86% and 59%, respectively. However, low patient numbers across both surveys limit further comparison and conclusions.

A different picture emerges when we look at patients with mild/moderate haemophilia. In the previous survey, 47% of respondents indicated they would perform ITI for patients with mild/moderate haemophilia and HR inhibitors: just one-third of these patients underwent ITI in the current survey (all failed, two were also on emicizumab prophylaxis).

Our findings indicate that while ITI is still considered a mainstay of treatment for many patients with HA with inhibitors – particularly those with more severe disease or higher inhibitor titres – a change in the approach to both ITI and prophylaxis has occurred since the previous survey. While the 2016 survey noted an 'emerging trend' towards the use of lower-dose regimens,¹⁷ the current survey suggests this trend is becoming the standard, with lower or less than daily dosing (often in combination with emicizumab prophylaxis) becoming commonplace across the spectrum of disease severity. This is in agreement with recent literature on inhibitor management, published since the launch of emicizumab in 2018.^{20–24} However, it should also be noted that VWF-containing products were considered to be a viable first-line treatment option – seemingly not influenced by availability of emicizumab – in many of the centres surveyed. This suggests that a clearly defined consensus regarding the first-line standard of care has yet to emerge. Though not reported, most respondents likely follow the Atlanta protocol, being the only published ITI regimen with less than daily dosing in combination with emicizumab prophylaxis.²⁴

While the results of our survey revealed a clear trend of less than daily dosing of ITI supported by prophylaxis, regional differences in the recommended daily dose suggest that we need to exercise caution when interpreting this outcome. In fact, all respondents indicated that they would initiate prophylaxis during ITI, with initiation being guided by bleeding patterns. Again, respondents indicated a strong preference for emicizumab prophylaxis with ITI when available and reimbursed. This suggests that the use of novel products either in place of or in combination with ITI is frequently guided by cost and availability. Emicizumab is currently not available in Turkey. While our survey does not include centres outside the Europe/Middle East region, the results presented here would likely be very different if we had included centres in lower-resource countries.

In terms of ongoing treatment in the case of a failed first ITI attempt, we are again seeing an increasing acceptance of emicizumab prophylaxis in this setting, with 93.8% of respondents indicating that they would consider prophylaxis with emicizumab after a failed first ITI attempt. The choice for subsequent ITI attempts was strictly related to the condition of the patient. However, the high rate of failed ITI in patients with VHR inhibitors shown in this survey represents a challenge/unmet need. Questions remain as to whether less-intensive

protocols with concurrent emicizumab prophylaxis offer any benefit in this population. However, the benefits of prophylaxis in patients with poor ITI prognosis are clear, and new innovative strategies are needed to achieve immunotolerance.¹⁰

Questions also remain regarding the extent to which ITI is important for patients with mild/moderate HA, as in many of these patients inhibitors disappear spontaneously. Most respondents would provide emicizumab to protect against bleeds in this population, and indicated that the likelihood of initiating ITI would be dependent on the inhibitor response (LR vs HR). In this context, it seems as if ITI remains an option for patients with mild/moderate HA. It should also be noted that inhibitor disappearance does not always equal sustained response, which further underlines the value of tolerance. Notably, literature indicates an anamnestic response in up to 35% of these patients when re-challenged.^{25,26} Another important issue to be settled, according to our findings, is the definition of success in mild/moderate HA.

So while there is a general consensus among experts that ITI remains the treatment of choice for many patients with inhibitors, emicizumab has emerged as an alternative, offering improved (e.g. vs BPA) prophylaxis.^{20–23,27,28} As such, emicizumab prophylaxis is currently considered as part of an ITI protocol that can reduce the burden of ITI on the patient and family by enabling lower dosing protocols and less-intensive FVIII regimens.^{24,29–31}

With increasing acceptance of alternatives to ITI and a greater range of treatment options, healthcare providers will increasingly tailor treatment to the needs of the specific patient based on risk, disease severity, and phenotype. While many clinicians would still initiate ITI, particularly in patients with more severe disease with HR inhibitors, our survey suggests that a greater consideration of the alternatives based upon the likelihood of ITI success/failure, often using a lower ITI dosing schedule in combination with prophylaxis, is now viable across the disease severity spectrum. It should however be noted that while the increased availability of new agents is presenting physicians with an alternative to ITI in some patients, and offering an opportunity to delay ITI in others with limited venous access, availability of emicizumab, the only new product licenced so far, is far from universal, with several of our survey respondents indicating access issues.

5 | CONCLUSION

ITI remains a mainstay for haemophilia treatment, but emicizumab 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.

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CONFLICT OF INTEREST

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Original survey data may be available by request to the corresponding author.

DATA AVAILABILITY STATEMENT

Original survey data may be available by request to the corresponding author.

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SUPPORTING INFORMATION

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