



The use of tranexamic acid for on-demand and prophylactic treatment of hereditary angioedema—A systematic review

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Abstract

Hereditary angioedema (HAE), caused by inherited deficiency of C1 esterase inhibitor (C1-INH), is characterized by recurring subcutaneous and/or submucosal edema. Although its efficacy remains controversial, tranexamic acid (TXA) is used to treat HAE in some countries. We analyzed TXA as an on-demand and prophylactic treatment in patients with HAE. Published data were systematically sourced from PubMed and Embase. All retained articles underwent grading/bias assessment using the “SIGN” grading system, and the quality of retained studies was determined following assessment of design and methodology. Of 353 studies identified, 31 were included. On-demand treatment and prophylactic treatment were assessed in five (N = 103) and 28 studies (N = 231), respectively. The majority of studies (80%) demonstrated that on-demand TXA was ineffective for skin, abdominal, or laryngeal swellings. In a single randomized controlled trial, the median time to relief of symptoms was 2 and 12 hours for icatibant and TXA, respectively ($P < 0.001$). For prophylaxis, while ~50% of case series, case reports, and observational studies reported beneficial effects of TXA, newer therapies, for example, icatibant and pdC1-INH, were more effective. One study found that breakthrough attacks during TXA prophylaxis lasted significantly longer compared with C1-INH (median time to resolution; 7 vs 3 hours, $P = 0.016$). Many studies failed to report safety data (16/31, 52%); however, pruritus, vomiting, and diarrhea were noted in some patients. There is no evidence for on-demand use of TXA in HAE and limited evidence for prophylaxis. While TXA may be more beneficial than no treatment, newer, more effective therapies should be used when available.

KEYWORDS

C1 inhibitor, hereditary angioedema, on-demand, prophylaxis, tranexamic acid

1 | BACKGROUND

Hereditary angioedema (HAE) is an autosomal dominant disorder most commonly caused by an inherited deficiency of C1 esterase inhibitor (C1-INH), a protein of the complement system.^{1,2} HAE type

I, occurring in ~85% of cases, is caused by deficiency of C1-INH while HAE type II, occurring in ~15% of cases, results from dysfunction of the C1-INH protein.³ HAE of unknown origin (HAE-U) occurs in a minority of patients who experience symptoms; however, the underlying genetic mutation remains unknown. In other cases, HAE

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symptoms are considered to be caused by genetic mutations of factor XII, plasminogen,⁴ or angiotensin-1.⁵ As such, diagnosis/treatment remains a challenge.⁶ HAE is characterized by recurrent episodes of localized subcutaneous (SC) or submucosal edema lasting for 2-5 days that occurs primarily in the extremities, face, genitals, trunk, and abdomen.⁷ Laryngeal edema (approximately 1% of all HAE type I and II attacks) may occur at any time and is potentially life-threatening.⁷⁻⁹

Numerous treatment options are available for HAE; these include on-demand treatment options for management of acute attacks (eg, C1-INH replacement therapy,¹⁰ kallikrein inhibitors [ecallantide],¹¹ bradykinin receptor antagonists [icatibant¹²]) and long-/short-term prophylactic treatment to reduce the frequency and/or severity of HAE attacks, for example, C1-INH replacement therapy, attenuated androgens,¹³ and antifibrinolytics¹⁴ (Figure 1). C1-INH has demonstrated considerable efficacy and safety, and while androgens may be effective in some patients, they are associated with side effects, particularly in women and children.¹⁵ Table 1 shows the different treatment options that are used in Japan as recommended by the Japanese Association for Complement Research. Three options are used for on-demand and prophylactic treatment; the antifibrinolytic tranexamic acid (TXA), C1-INH replacement therapy, and the attenuated androgen, danazol.^{16,17} Of these, plasma-derived (pd) C1-INH is specifically licensed for the treatment of HAE,¹⁸ while TXA is licensed for urticaria and swelling, not necessarily caused by HAE.¹⁹

Tranexamic acid was first reported by Okamoto and Okamoto in Japan, who highlighted its potent inhibitory effects on fibrinolysis.²⁰ A synthetic derivative of lysine, TXA works by binding to plasminogen molecules. This in turn inhibits the formation of plasmin, which is normally inhibited by C1-INH. As such, TXA blocks the activation of the complement system and immune cells such as neutrophils, thus attenuating the symptoms of HAE.²¹ TXA can be administered orally or intravenously¹⁹ and is utilized in the management of perioperative bleeding,²² trauma,²³ and also in the treatment of melasma.²⁴ Although TXA is generally well tolerated with a low adverse event rate, there are concerns regarding lack of efficacy compared with

TABLE 1 Treatment options for hereditary angioedema in Japan

	Acute laryngeal attacks	Acute SC attacks	STP	LTP
Tranexamic acid	-	+	-	+
C1-INH	+	+	+	-
Danazol	-	-	-	+

C1-INH, C1 esterase inhibitor; LTP, long-term prophylaxis; SC, subcutaneous; STP, short-term prophylaxis.

other widely available treatment options, that is, C1-INH replacement therapy and attenuated androgens.²⁵ Moreover, many patients continue to experience intermittent swellings and require additional use of rescue medication while on TXA prophylaxis.²⁶ Importantly, clinical data have failed to demonstrate a dose of antifibrinolytics that is effective in a large number of patients, and furthermore, side effects including nausea, fatigue, and diarrhea have been observed in some observational studies.²⁷ The therapeutic efficacy of TXA is determined on an individual basis, and each patient should be treated with the lowest effective dose.

A retrospective survey in Japan found that TXA was used for prophylaxis in 39.2% of patients.²⁸ This is a nontypical situation compared with many other regions and is due to limited availability of HAE-specific therapies. Furthermore, self-administration of pdC1-INH is not licensed in Japan, and not all hospitals keep adequate stocks, which can make accessibility difficult for some patients.²⁹ Importantly, TXA is a more suitable option for patients in whom androgens are contraindicated, for example, women and expectant mothers.¹⁵ In addition, androgens have been associated with numerous anabolic/androgenic side effects; therefore, treatment requires careful monitoring of patients for the detection of adverse events.¹⁵

Worldwide, several other clinically effective options for the treatment of HAE are available. Recombinant C1-INH has proven to be effective for on-demand treatment, reducing the time to relief of symptoms from 152 to 90 minutes, compared with placebo ($P = 0.031$).³⁰ Similarly, ecallantide and icatibant have demonstrated

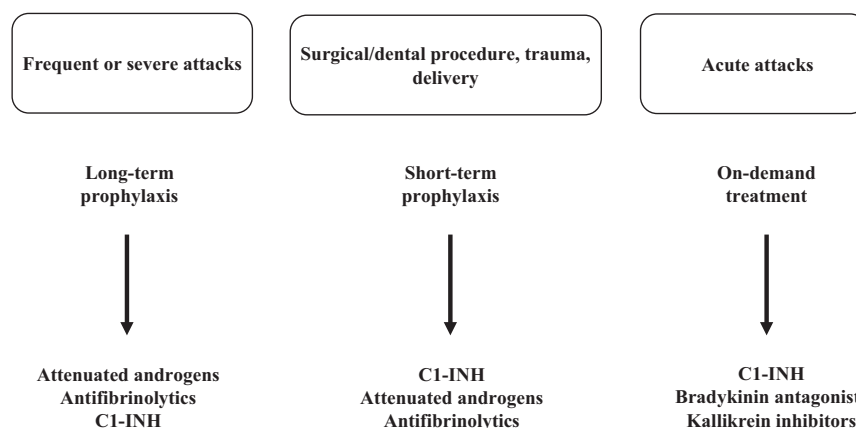


FIGURE 1 The therapeutic landscape in Japan. In Japan, there are several options available for on-demand treatment and prophylaxis of hereditary angioedema

significantly reduced symptom severity compared with placebo.^{31,32} In addition, the long-term safety and efficacy of pdC1-INH have been evaluated using real-world patient registry data, which showed that pdC1-INH administration reduces the rate of attacks and is associated with an excellent safety profile.³³ Recently, SC injection of C1-INH has also been approved for long-term prophylaxis (LTP) in adults and adolescents. Data from the COMPACT trial demonstrated a favorable safety profile and a significantly reduced rate of attacks with self-administered SC C1-INH, which also resulted in near-normal C1-INH levels.³⁴

Given the advent of numerous effective therapies in recent years, the aim of this systematic review was to analyze the evidence for the use of TXA as an on-demand and/or prophylactic treatment option in patients with HAE. The efficacy of TXA for the treatment of HAE was assessed through the evaluation of safety and efficacy data from clinical trials, observational studies, and case reports.

2 | METHODS

2.1 | Search strategy

This review was constructed based on two research questions: (a) Does the evidence suggest that TXA is an effective strategy for the prophylactic/on-demand treatment of HAE? and (b) Should TXA continue to be used even though newer and more effective therapies are available? Searches were performed using PubMed to identify published clinical data from inception to May 10, 2018. The following search terms were used: “hereditary angioedema” OR “hereditary angio-neurotic edema” AND “tranexamic acid.” The main searches were complemented by searching the Cochrane Library; however, no additional studies were identified. Searches were also performed on Embase to identify additional studies not found in PubMed.

2.2 | Selection of studies

Titles and abstracts of all retrieved articles were assessed to identify eligible studies. Relevance was defined according to inclusion and exclusion criteria listed in Table 2. Eligible studies were published in English, conducted in human subjects, and contained original clinical data on the efficacy or safety of TXA in type I/type II HAE. Narrative and systematic review articles were not included. Titles and abstracts were initially screened followed by full-text analysis in cases of uncertainty.

2.3 | Data extraction and assessment

The following data were extracted: type of study, patient population, efficacy outcomes, for example, prevention of attacks or alleviation of symptoms, and safety outcomes, for example, adverse reactions or side effects. All retained articles underwent grading and bias assessment using the “SIGN” grading system; the quality of studies was determined following assessment of study design

TABLE 2 Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
A. Articles published in English	F. Articles in any language other than English
B. Human subjects	G. Nonclinical reports (eg, animal models, in vitro or ex vivo experimental studies)
C. Clinical study	H. Guidelines, meta-analyses, systematic reviews, literature reviews, editorials, or commentaries
D. Efficacy or safety data on TXA	I. Articles not reporting original data on tranexamic acid
E. HAE type I and type II	J. Studies on HAE type III

HAE, hereditary angioedema; TXA, tranexamic acid.

and methodology³⁵ (Table S1). Bias was defined as follows: performance bias, that is, differences in treatment given to comparison groups; selection bias, that is, significant differences in baseline characteristics between groups; detection bias, that is, small sample size; recall bias, that is, data/outcomes based on subjective memory; reporting bias, that is, selective outcome reporting that favors one group over another. Studies were judged to have a low, acceptable, or high risk of bias and a quality grading between 1 and 3 (Table S1).

Using this system, RCTs were given a score of 1 (the highest rating), whereas case reports were given a score of 3 (the lowest rating). All other articles, including observational studies, were given a score of 2. Studies were further up or downgraded based on the robustness of the study design, whereby ++, +, or - was added, to denote low, acceptable, or high risk of bias, respectively.

3 | RESULTS

3.1 | Included Studies

Figure 2 shows identification and selection of relevant studies for the present systematic review. A total of 353 studies were originally identified; one duplicate article was found, and 318 articles were excluded based on screening of titles/abstracts. Reasons for exclusion based on initial screening were type III HAE (N = 37), non-English articles (N = 28), no original data on TXA (N = 80), and nonclinical studies (N = 173). In cases of uncertainty (N = 35), the article was retained for full-text analysis, and any meeting the exclusion criteria were subsequently rejected from the evidence base (N = 4; non-English articles [N = 2], nonclinical studies [N = 1], no original data on tranexamic acid [N = 1]). Thirty-one articles were retained overall.

The evidence base for this review was formed mainly of case reports/series (N = 16)^{36–51} and observational studies (N = 10).^{52–61} There was one RCT,⁶² two crossover studies,^{63,64} one questionnaire,⁶⁵ and one survey.⁶⁶ Three studies evaluated TXA in on-demand treatment,^{60,62,65} 26 evaluated prophylactic

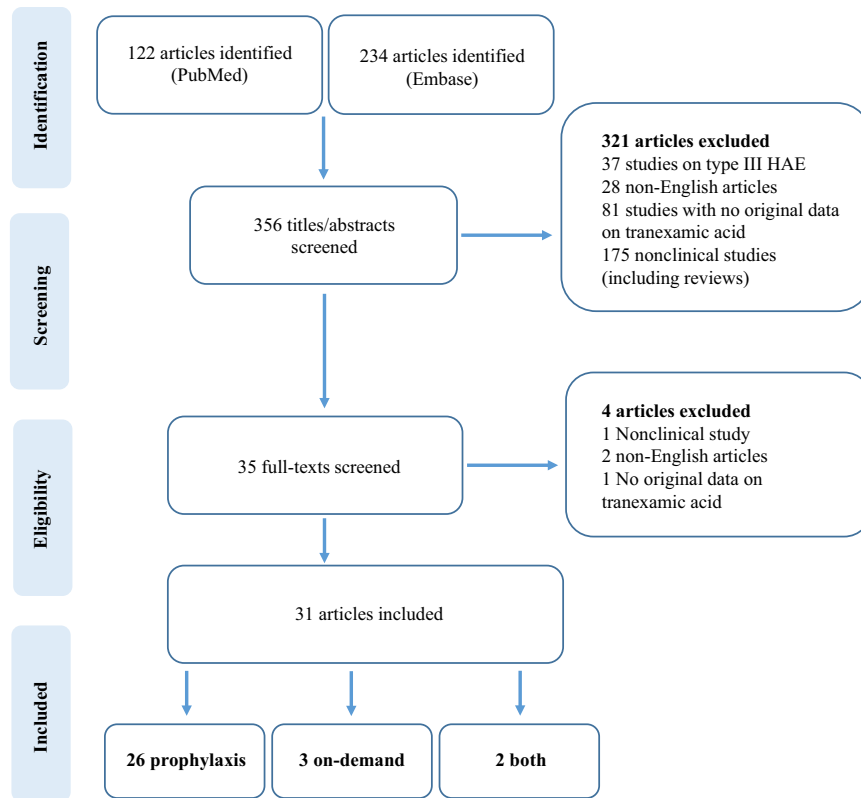


FIGURE 2 PRISMA flow diagram

treatment,^{36–45,47–59,63,64,66} and two studies looked at both.^{46,61} The number of patients treated with on-demand TXA overall was 103, and the number of patients treated prophylactically was 231.

3.2 | Bias Assessment

Two studies were assigned a grading of 1, indicating a weak-to-moderate evidence base overall. Several of the included studies were case reports with no valid comparator; these reports were assigned a quality grading of 3 and did not undergo bias assessment (N = 16). The majority of the observational studies were assigned a grading of 2+, meaning that they were deemed to have an acceptable risk of bias, apart from three studies.^{53,60,61} One randomized crossover study was assigned a grading of 1–,⁶³ while the other nonrandomized crossover study was assigned a grading of 2–.⁶⁴ A single RCT was graded as 1+, with an acceptable risk of bias overall despite industry sponsorship. All observational studies are at risk of reporting bias as there is no control of confounding variables, and observed effects cannot be conclusively attributed to therapeutic interventions. Selection bias was identified in 80% of studies that underwent bias assessment; this was largely due to the absence of defined inclusion/exclusion criteria. Recall bias was identified in 40%, including studies that relied on patient-reported data. Detection bias due to small sample size was identified in 87% of the studies included in the assessment. Industry involvement was identified in 27% (Table S1).

3.3 | Efficacy of tranexamic acid for on-demand treatment

Studies assessing the efficacy of TXA for on-demand treatment of HAE attacks are listed in Table 3. The corresponding SIGN level is also shown; there was one RCT, two observational studies, one questionnaire, and one case series. Overall, the evidence base for on-demand treatment was moderate-low; the majority of studies were assigned a quality grading of 2, and all studies demonstrated that TXA was effective in a subpopulation of patients and was less effective than other on-demand treatments.

The strongest evidence for the reduced efficacy of TXA comes from a single RCT in 74 patients; the study by Cicardi et al⁶² demonstrated that icatibant was significantly more effective than TXA in treating acute HAE attacks. The median time to clinically significant relief of symptoms was 2 and 12 hours for icatibant and TXA, respectively. Further, the percentage of patients with clinically significant relief of symptoms at 4 hours after the start of treatment was 80% in the icatibant group, compared with 31% in the tranexamic acid group (both $P < 0.001$).⁶²

In a more recent study of on-demand TXA treatment, Nordenfelt et al⁶⁵ used a patient questionnaire to analyze the efficacy of a number of treatments, including C1-INH, androgens, and TXA. Participants were asked to grade the efficacy of treatment on a 4-step scale, 0 being no effect and 3 being very good. Although data were based on patient-reported outcomes, TXA was graded 1 for skin

TABLE 3 Safety and efficacy of tranexamic acid for the treatment of acute hereditary angioedema attacks

Study/type (Total number of patients in study)	Patient population	Population age (years)	No. treated with TXA	TXA dose/ duration of treatment	Efficacy	Safety	SIGN grade
Nordenfelt et al (2016) ⁶⁵ Questionnaire N = 102	HAE type I and type II	Range: 1-87	15	Not reported	TXA was graded as 1 (poor) for skin swellings and as 0 (ineffective) on abdominal or laryngeal attacks	NR	2+
Zanichelli et al (2015) ⁶⁰ Observational study N = 227	HAE with C1-INH deficiency	43 (IQR 29-54)	14	500 mg or 1 g every 5-6 h orally	Median duration of attacks: Icatibant—8 h pdC1-INH—11.5 h TXA—38 h Untreated—45 h	NR	2–
Zanichelli et al (2011) ⁶¹ Observational study N = 56	HAE with C1-INH deficiency	Median: 39.2	29	Recommendation for peripheral/mild attacks—1 g, 20 mg/kg for children, every 4 h orally	Median duration of attacks: TXA vs pdC1-INH—1.79 d vs 1.10 d ($P < 0.01$) TXA vs no treatment—1.79 d vs 1.85 d ($P > 0.05$)	NR	2–
Cicardi et al (2010) ⁶² RCT N = 74	HAE with C1-INH deficiency	Median: 40.4-41.9	38	3 g daily for 2d	Median time to Clinically significant relief of symptoms: icatibant vs TXA (2 vs 12 h; $P < 0.001$)	Five patients (14%) receiving icatibant and four patients (11%) receiving TXA had a total of nine and six drug-related AEs, respectively	1+
Ohela et al (1976) ⁴⁶ Case series N = 7	HAE with C1-INH deficiency	Range: 24-66	7	1-1.5 g 2 or 3x/d	TXA had a beneficial effect in 6/7 patients	Transient elevation of GPT, fatigue, and dizziness	3

AE, adverse events; d, days; C1-INH, C1 esterase inhibitor; GPT, glutamic pyruvic transaminase; HAE, hereditary angioedema; IQR, interquartile range; NR, not reported; pd, plasma derived; RCT, randomized controlled trial; TXA, tranexamic acid.

swellings, indicating poor efficacy, and was ineffective for abdominal and laryngeal attacks. In addition, androgens had poor efficacy while C1-INH had a more positive effect and better grading overall. Two observational studies also showed that newer therapies were significantly more effective than TXA for the treatment of HAE attacks. Zanichelli et al⁶¹ reported that pdC1-INH significantly improved attack duration compared with TXA (median duration of attacks: 1.10 days pdC1-INH; 1.79 days TXA; $P < 0.01$). Importantly, the median duration of attacks was not significantly different compared with those that received no treatment (1.79 vs 1.85 days, respectively; $P > 0.05$). The results of this study were echoed by Zanichelli et al⁶⁰; the median duration of attacks following icatibant (8 hours) or pdC1-INH (11.5 hours) treatment was significantly lower compared with TXA (38 hours) or untreated patients (45 hours). In contrast, a case series by Ohela et al⁴⁶ found that TXA had a beneficial effect in six out of seven patients that were treated on-demand.

3.4 | Efficacy of tranexamic acid for prophylaxis

Studies assessing the efficacy of prophylactic treatment with TXA for prevention of HAE attacks are shown in Tables 4 and 5 along with the corresponding SIGN level. A total of 24 studies assessed the efficacy of TXA for LTP in patients with HAE; of these, 14 (58%) reported some positive effects of TXA (Table 4). There were 10 case reports and four case series, seven observational studies, two cross-over studies, and one survey. The evidence base for prophylactic use of TXA is moderate-weak. Although there were several studies demonstrating a beneficial effect of prophylactic treatment with TXA, the majority of studies were deemed to be low-level evidence and assigned a SIGN grade of 2 or 3. Our study identified ten reports (42%) demonstrating that TXA was ineffective or led to worse outcomes following long-term prophylactic treatment in patients with HAE.

3.5 | Long-term prophylaxis

Figure 3 shows the proportion of case reports, case series, and observational studies that reported better/worse outcomes or no change in response to TXA LTP. The most robust data were reported in a randomized crossover study; Blohme et al⁶³ found that 3/5 patients responded positively to TXA prophylaxis compared with placebo. One patient experienced abdominal pains and skin edema for the duration of treatment, and TXA had to be withdrawn due to severe vomiting. Another nonrandomized crossover study showed that TXA led to a complete or almost complete cessation of attacks in 7/18 patients (39%),⁶⁴ and TXA modestly reduced the frequency of attacks in four patients; however, these attacks were of markedly reduced severity.

3.6 | Beneficial outcomes following TXA treatment

Several observational studies support the efficacy of TXA. Cicardi et al⁵⁴ reported that 70% of patients experienced a reduced frequency of attacks in response to TXA. Aberer et al⁶⁶ showed that the attack rate for 43 patients on LTP with TXA was an average of 1.6 attacks per year, compared with 1.5 for androgens and 2.3 attacks per year for patients on C1-INH; these differences were not significant. However, the breakthrough attacks reported during TXA prophylaxis lasted significantly longer compared with C1-INH ($P = 0.016$). Gomez-Traseira et al⁵⁶ also showed that the median number of attacks was higher in patients receiving C1-INH compared with TXA and danazol over the course of a year (14.0 vs 3.5 vs 2.5, $P = 0.003$). Importantly, the authors note that C1-INH was administered to more severe cases overall. Further observational data suggested that TXA can reduce attack frequency in some cases by >75%⁵⁹ and reduced the frequency and/or severity of attacks in approximately 20 patients.^{36,57} The above findings are further corroborated by several case reports, which documented a decrease in the frequency and severity of attacks in response to LTP with TXA^{41,43,49}; several other patients were kept asymptomatic while on TXA prophylaxis.^{45,46,51}

3.7 | No change following TXA treatment

Three observational studies demonstrated that TXA is less effective than androgens in reducing the frequency of attacks. Agostoni et al⁵² reported that danazol/stanozolol was effective in reducing HAE attacks in 97% (57/59) of patients compared with just 26% (7/27) of patients receiving TXA. Furthermore, Zanichelli et al⁶¹ were not able to demonstrate any significant difference in the frequency and duration of attacks (number of attacks per year/duration [days]) associated with use of attenuated androgens (7.7/1.47), TXA (8.1/1.59), or no prophylaxis (8.9/1.68). An appraisal of LTP in Denmark found that 3/5 patients discontinued TXA due to lack of efficacy.⁵³ In addition, a number of case studies reported the noneffectiveness of TXA for LTP, concluding that TXA was ineffective at reducing both the frequency and severity of attacks.^{37,39,44}

3.8 | Worse outcomes following TXA treatment

Four case reports/series reported detrimental effects of TXA. Farkas et al³⁸ demonstrated that TXA was ineffective during pregnancy; in this case, the frequency of the patient's attacks increased and she eventually miscarried on week nine. Three other case reports showed that TXA prophylaxis resulted in increased attack frequency,⁵⁰ adverse effects leading to discontinuation,⁴⁸ and recurrent laryngeal edema.⁴²

3.9 | Short-term prophylaxis (STP)

Four studies looked at the use of TXA in STP (Table 5). Farkas et al⁵⁵ performed a long-term survey of STP for prevention of perioperative attacks. They demonstrated that the proportion of patients experiencing an HAE attack despite STP was highest following TXA treatment (33% of patients) compared with danazol (13%) or pdC1-INH (6%).⁵⁵ In contrast, Sheffer et al⁵⁸ looked at STP in 14 patients undergoing surgical procedures and found that TXA was adequate for prophylaxis in all cases, as no attacks or prodromal symptoms were observed. Two case reports also documented uncomplicated procedures; Hermans et al⁴⁰ reported a tonsillectomy with no edema crisis and the level of C1-INH was increased to 78% of normal on the day of surgery; this was in conjunction with C1-INH and danazol. Owatari et al⁴⁷ administered TXA for STP during tooth extraction and reported no acute attacks.

3.10 | Safety profile of TXA

Many studies failed to report any safety data (15/31, 48%; Tables 3-5). Reported side effects in response to on-demand TXA treatment included fatigue and dizziness in a limited number of patients. Most of the trials that reported safety data in response to TXA LTP did not identify any adverse events; however, abdominal discomfort, vomiting, pruritus, vertigo, and diarrhea were reported in some patients.

4 | DISCUSSION

This systematic review evaluated data on the use of TXA for on-demand ($N = 5$) and prophylactic treatment ($N = 28$) of HAE caused by C1-INH deficiency. We found that there is limited evidence for the use of TXA as an on-demand treatment and that it is generally inferior to other treatments such as pdC1-INH and icatibant. The evidence for the use of TXA in prophylaxis varied; for long-term prophylaxis, thirteen studies demonstrated some TXA efficacy, that is, reduced attack frequency and/or severity; however, these data are contradicted by studies demonstrating that TXA was ineffective in some patients and was less effective than other treatment such as C1-INH. Importantly, these data also came from small, noncontrolled studies. For short-term prophylaxis, TXA was largely used successfully during dental procedures or perioperatively to prevent acute attacks; however, larger, controlled trials are necessary to

TABLE 4 Safety and efficacy of tranexamic acid for the long-term prophylactic treatment of hereditary angioedema

Study/type (Total number of patients in study)	Patient population	Mean Population age (years)	No. treated with TXA	TXA dose/ duration of treatment	Efficacy	Safety	SIGN grade
Good outcome following TXA treatment							
Blohme et al (1972) ⁶³ Crossover study N = 3	HAE with 1-INH deficiency	49-73	5	2-3 tablets (0.5 g each) 3 × daily	Patient 1: No reduction in frequency; however, attack severity is reduced Patient 2: A reduction in attack severity but less effective than EACA Patient 3: TXA led to reduced frequency and severity Patient 4: TXA led to alleviation of all symptoms Patient 5: TXA had limited efficacy	Diarrhea and flatulence; no serious side effects	1+
Sheffer et al (1972) ⁶⁴ Crossover study N = 18	HAE with C1-INH deficiency	Range: 12-72	18	2 × 0.5 g 3×/d	Seven patients experienced a complete/almost complete cessation of attacks while on TXA compared with treatment. Difference in frequency of attacks between TXA and placebo (<i>P</i> < 0.005)	Minimal side effects; pruritus, abdominal discomfort, diarrhea	2–
Aberer et al (2017) ⁶⁶ Survey N = 448	HAE with C1-INH deficiency	40.8	43	Mean (SD) duration: 3.4 (1.8) y	The attack frequency ^a was as follows: 1.6 attacks/y for TXA compared with 1.5 for androgens and 2.3 for C1-INH; breakthrough attacks were significantly longer for TXA compared with C1-INH (<i>P</i> = 0.016)	NR	2+
Gómez-Traseira et al (2015) ⁵⁶ Observational study N = 112	HAE with C1-INH deficiency	37.5	9	6.7 g (3.5-14.0) weekly over 1 y	The median number of attacks while on LTP was 3.5 for patients on TXA, 2.5 for patients on danazol and 14.0 for patients on C1-INH (<i>P</i> = 0.003)	NR	2+
Wintenberger et al (2014) ⁵⁹ Retrospective observational study N = 37	HAE type I and II	34	12/6 (HAE with/without C1-INH deficiency)	Median dose: 2.5/3 g/d Median duration: 34/30 mo	Average no. of attacks (range) 6 mo before/after commencing TXA: 14 (3-48)/7 (0-24) (type I) 16 (6-50)/6 (4-15) (type II)	No serious AEs	2+
Nowicka et al (2007) ⁵⁷ Observational N = 39	HAE with C1-INH deficiency	9-57	8	0.25-2 g/d over 1-2 mo	TXA prophylaxis led to noticeable clinical results	No adverse events	2+

(Continues)



TABLE 4 (Continued)

Study/type (Total number of patients in study)	Patient population	Mean Population age (years)	No. treated with TXA	TXA dose/ duration of treatment	Efficacy	Safety	SIGN grade
Cicardi et al (1982) ⁵⁴ Observational N = 104	HAE with C1-INH deficiency	3-80	34	1.5-3 g/d; 1-5 y	Frequency of attacks reduced in 70%, and one patient was kept symptom-free	No side effects	2+
Agostoni et al (1978) ³⁶ Case series N = 16	HAE with C1-INH deficiency	10-48	16	1.5-3 g/d	Complete remission or reduction in frequency/ severity of attacks seen in 12 patients; not effective in four leading to withdrawal	No side effects	3
Ohela et al (1976) ⁴⁶ N = 7 Case series	HAE with C1-INH deficiency	24-66	3	1 g 2 or 3x/d	2/3 patients were kept symptom free; one patient had a moderate response	One patient had to stop TXA due to severe fatigue, nausea, and vertigo	3
Sim et al (2017) ⁴⁹ Case report N = 1	Type II HAE with <i>SERPING1</i> mutation	24	1	NR	Continued HAE-related symptoms, though both the frequency and severity of attacks had lessened	NR	3
Milingos et al (2009) ⁴³ Case report N = 1	HAE with C1-INH deficiency	22	1	TXA 500 mg 2x/d	Attacks were managed successfully in conjunction with danazol and C1-INH	NR	3
Montalto et al (2007) ⁴⁵ Case report N = 1	HAE type II	19	1	250 mg 3x/d for 6 mo	The patient experienced clinical improvement and became asymptomatic after 6 mo of therapy	NR	3
Williams et al (2007) ⁵¹ Case report	HAE type II	15	1	NR	The patient became asymptomatic after initiation of TXA	NR	3
Karim et al (2004) ⁴¹ Case report N = 1	HAE with C1-INH deficiency	10	1	NR	The patient was started on TXA, and at outpatient review 3 mo later, frequency and severity of episodes had decreased	NR	3
No change following TXA treatment							
Agostoni et al (1993) ⁵² Observational study N = 243	HAE with C1-INH deficiency	3-89	27	1.5-3 g/d	Clinical effectiveness (reduction in frequency of attacks): Danazol/stanozolol— 57/59 patients TXA—7/27 patients	No side effects	2+
Bygum et al (2014) ⁵³ Observational study N = 80	HAE with C1-INH deficiency	Range: 22-41	3	1-3 g/d, 6-11 y	Five patients started TXA at study entry; three stopped during observation period due to lack of efficacy	No serious AEs	2-

(Continues)

TABLE 4 (Continued)

Study/type (Total number of patients in study)	Patient population	Mean Population age (years)	No. treated with TXA	TXA dose/ duration of treatment	Efficacy	Safety	SIGN grade
Zanichelli et al (2011) ⁶¹ Observational study N = 47	HAE with C1-INH deficiency	39.2 (11-93)	6	1.5-3 g/d	Median attacks per year/duration (d): Attenuated androgen: 7.7/1.47 TXA: 8.1/1.59 No prophylaxis: 8.9/1.68	NR	2-
Csuka et al (2011) ³⁷ Case series N = 4	HAE with C1-INH deficiency and celiac disease	5-16 (at diagnosis of HAE)	4	500-2000 mg/d	LTP with TXA was ineffective in three cases; one patient experienced transient improvement	NR	3
Hamilton et al (1977) ³⁹ Case report N = 1	HAE with C1-INH deficiency	29	1	0.5 g/d	Frequency/severity of attacks has not changed significantly since starting TXA	NR	3
Molina et al (1977) ⁴⁴ Case report N = 1	HAE with C1-INH deficiency	35	1	1.5 g/d	TXA not effective	NR	3
Bad outcome following TXA treatment							
Van kester et al (2017) ⁵⁰ Case report N = 1	HAE with C1-INH deficiency	55	1	500 mg 2x/d	Attacks increased in frequency and the patient required acute C1-INH	Wheals and angioedema increased in frequency	3
Martinez-Sauger et al (2016) ⁴² Case report N = 1	HAE with C1-INH deficiency	17	1	NR	The patient was switched to LTP with danazol due to recurrent laryngeal edema while on TXA	NR	3
Farkas et al (2015) ³⁸ Case report N = 1	HAE with C1-INH deficiency	34	1	1.5 g/d	The patient miscarried while on LTP with TXA and her symptoms were not adequately controlled	No thrombotic adverse events	3
Pedrosa et al (2014) ⁴⁸ Case series N = 2	HAE with C1-INH deficiency	NR	2	NR	Patient 1: TXA failed to prevent acute attacks Patient 2: Adverse effects led to withdrawal	Weakness, vomiting, and steatohepatitis in one patient	3

AE, adverse events; C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; NR, not reported; SERPING1, serpin family G member 1; SD, standard deviation; TXA, tranexamic acid.

^aAttack frequency was calculated by dividing the number of attacks by the total duration of treatment.

confirm its efficacy. Just over half of the included studies reported safety data, and notably, much of the evidence for the use of TXA as an on-demand or prophylactic treatment came from lower level observational studies and case reports, and only one RCT was included.

Guidelines published by the Hereditary Angioedema International Working Group (HAWK) and the World Allergy Organization (WAO) state that acute HAE attacks should be treated with C1-INH icatibant and ecallantide; antifibrinolytics such as TXA are not

recommended for the treatment of acute HAE attacks and are strongly recommended against in the WAO guidelines because of inefficacy.^{67,68} The majority of studies included in this review are supportive of the recommendations made by HAWK and the WAO.

This review demonstrates that there is very limited data on the efficacy of TXA as an on-demand treatment. Only a single RCT was identified, and results from this study showed that TXA took six times longer to induce clinically significant relief of symptoms compared with icatibant.⁶² These data were supported by evidence from

TABLE 5 Safety and efficacy of tranexamic acid for the short-term prophylactic treatment of hereditary angioedema

Study/type (Total number of patients in study)	Patient population	Population age (years)	No. treated with TXA	TXA dose/duration of treatment	Efficacy	Safety	SIGN grade
Farkas et al (2012) ⁵⁵ Observational study with long-term follow up N = 137	HAE with C1-INH deficiency	41.3 (18.5-81.2)	9	20-40 mg/kg/d orally started 5 d before and continued for additional 2 d after intervention	Proportion of interventions followed by edema despite STP: Danazol—5/38 (13%); TXA—3/9 (33%); pdC1-INH—5/87 (6%)	No treatment- related AEs	2+
Hermans et al (2012) ⁴⁰ Case report N = 1	HAE with C1-INH deficiency	29 y	1	1 g 3×/d throughout the perioperative period	TXA, in conjunction with C1-INH, enabled an uncomplicated tonsillectomy with no edema crisis	NR	3
Owatari et al (1995) ⁴⁷ Case report N = 1	HAE with C1-INH deficiency	82 y	1	NR	Prophylactic TXA administered before, during, and after tooth extraction was successful in preventing acute attacks	NR	3
Sheffer et al (1977) ⁵⁸ Observational study N = 14	HAE with C1-INH deficiency	14-54	14	1 g every 6 h beginning 48 h before surgery and continuing 48 h after surgery	TXA prophylaxis was adequate in patients undergoing orotracheal manipulation or general surgical procedures	No complications	2+

AE, adverse events; C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; NR, not reported; pd, plasma derived; TXA, tranexamic acid.

observational studies.^{60,61} Guidelines also state that either pdC1-INH (first-line) or androgens (second-line) should be used for LTP.⁶⁷ Similarly for STP, the guidelines do not make a specific recommendation for TXA use, stating that its efficacy in suppressing breakthrough attacks seems to be low.⁶⁷ The conflicting evidence generated by observational studies and case reports highlights the difficulty in drawing firm conclusions regarding the efficacy of TXA. While there were several observational studies and case reports supporting the lack of efficacy of TXA for prophylaxis, we also identified some studies demonstrating that TXA may be effective in some patients. Gomez-Traseira et al⁵⁶ found that patients receiving TXA experienced fewer attacks than those on C1-INH. Importantly, C1-INH was administered to patients with more severe disease. Reduction in the frequency of attacks as a measurement of response may provide more valuable data, as this is not affected by differences in the baseline frequency of attacks between patients on different treatments.

A previous systematic review on the management of HAE concluded that more comparative trials are required to provide convincing evidence of the benefit and safety of specific, potentially lifelong prophylactic therapy, including antifibrinolytics.⁶⁹ However, since publication of this report in 2012 no new RCTs have been conducted. TXA may be particularly useful for STP during tooth extraction and uncomplicated surgical procedures, as the majority of studies showed

that perioperative TXA prophylaxis provided adequate protection from attacks. Importantly, there is consensus that treatment should be individualized to each patient; therefore, for a limited number of patients who may benefit, TXA use is advocated.⁶⁸

On the whole, there are insufficient safety data on TXA in HAE. Somewhat outdated preclinical data suggested that long-term TXA administration at high doses led to tumor formation in the retina and liver,⁷⁰ while regulatory bodies state that TXA can be associated with vomiting, diarrhea, and hypersensitivity, and should not be used in patients with renal insufficiency.^{14,71,72} However, the findings of this review suggest that overall, TXA is generally well tolerated and based on equivalent efficacy is preferable to androgens. Importantly, as most of the safety data have been generated from case reports on individual patients, it is difficult to generalize these results to all patients with HAE, and to properly assess the safety of tranexamic acid, more robust clinical trials are required as well as long-term, real-world evidence.

5 | CONCLUSIONS

In certain countries, particularly Japan, TXA is an important treatment option for many patients with HAE, particularly for LTP. Although C1-INH has been demonstrated to be safe and

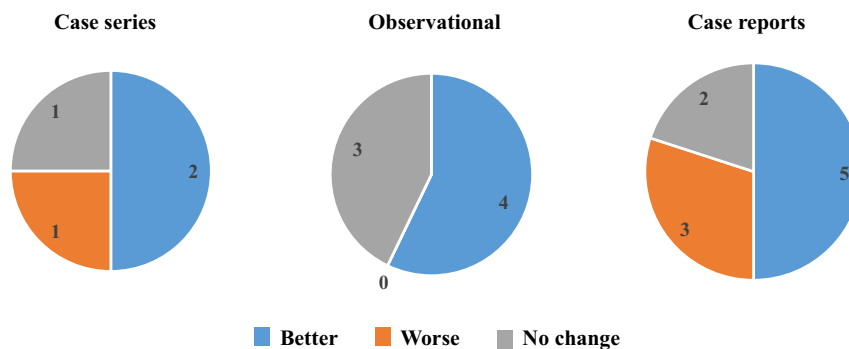


FIGURE 3 Efficacy of tranexamic acid in case studies/reports and observational studies. The proportion of case studies, case reports, and observational studies that reported better or worse severity/frequency of hereditary angioedema symptoms, or no change in response to tranexamic acid

effective,^{30,33} self-administration and LTP are not licensed, and accessibility to treatment is challenging for many patients in Japan.²⁹ In addition, awareness of HAE among physicians in Japan is low and the limited availability of effective therapies increases the burden of HAE.⁷³ Diagnosis of HAE worldwide can take an average of 8.3 years; this figure is thought to be much longer in Japan.^{29,73,74} While danazol is available for off-label use, it has been associated with numerous side effects, including virilization, headaches, depression, and acne. In addition, the risk of adverse events in response to androgens increases the longer the duration of treatment.¹⁵ Our findings suggest the need for increased awareness of available treatment options and an increase in the availability of more effective therapies. Published guidelines are in line with our findings and conclusions. TXA is not recommended for on-demand treatment or prophylaxis. This is particularly relevant in Japan, considering that alongside danazol, TXA is the only other option available for LTP. Neither treatment can be considered both safe and effective in the majority of patients with HAE. As such, these findings highlight a significant unmet need in Japan with regard to the paucity of clinically effective treatment options, and suggest the need for increased awareness among patients and physicians to ensure more options become available in the near future. The use of TXA is advocated in selected patients that have already been shown to benefit; however, it is likely that once more options become more widely available, the requirement for TXA in both on-demand and prophylactic treatment of HAE may be significantly reduced.

There are several limitations to this review, not least the lack of robust quantitative data generated from well-conducted RCTs. A large number of studies, particularly in prophylaxis, failed to report numerical data, stating only that TXA was either effective or ineffective at reducing symptoms and/or the frequency of attacks.^{37,39,41,49,50,57} Data generated from observational studies and case reports are inherently biased due to the lack of comparators and lack of control over confounding variables; these issues are much less likely to arise in RCTs. Finally, many studies did not report any safety data, which makes it difficult to draw firm conclusions regarding the safety of TXA in the HAE patient population.

The findings presented in this review highlight several conclusions. TXA may be more effective than no treatment, particularly for STP. However, the efficacy of TXA varies widely between patients, and in many cases, the effect of TXA is negligible. For on-demand treatment, there is clear evidence that newer therapies such as icatibant and pdC1-INH are more effective than TXA. Although there have been no direct comparisons between ecallantide and TXA, ecallantide might also be considered superior given its clear advantages when compared with no treatment. For prophylaxis, while some efficacy is observed in selected patients, TXA is inferior to many other options, including C1-INH replacement therapy. As such, there may be limited utility for TXA in STP prior to dental procedures and minor surgery; however, where available, newer, more effective therapies should be used in place of TXA for LTP.

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APPROVAL OF THE RESEARCH PROTOCOL

No human participant was involved in this study.

CONFLICT OF INTEREST

TH has received honoraria as an advisor for CSL Behring and Shire. MH has received honoraria as a speaker/advisor from BioCryst, CSL Behring, and Shire. He has also received institutional research funding from CSL Behring. KY has no competing interests. IO has received honoraria as a speaker/advisor from BioCryst, CSL Behring, and Shire.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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