The French Polidocanol Study on Long-Term Side Effects: A Survey Covering 3,357 Patient Years

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BACKGROUND, AIMS Short- and mid-term side effects of sclerotherapy, in particular with polidocanol (lauromacrogol 400), have been previously described in our registry of 12,173 sessions. The objective of this follow-up registry was to evaluate the long-term incidence of adverse events with polidocanol.

METHODS The physicians involved in the initial French registry were contacted and asked to partake in the follow-up survey. Initially included patients were controlled at the latest possible date to determine whether a complication had occurred after the end of the initial survey.

RESULTS Data on 1,605 patients included in the French registry were reviewed with a maximum follow-up of 60 months, covering 3,357 patient years. Five (0.4%) adverse events were observed in patients treated with liquid polidocanol and 46 (1.1%) in patients treated with polidocanol foam. The most frequent side effects were visual disturbances ($n = 14$), and the most severe were muscular vein thrombosis ($n = 8$). The onset of side effects was mostly observed directly after sclerotherapy or in the 6 months after (84% in the first year). One deep vein thrombosis recurrence occurred in a patient with heterozygote Factor V Leiden after stopping anticoagulant treatment (foam sclerotherapy).

CONCLUSIONS Foam sclerotherapy is a recognized reference method in the treatment of varicose veins of all types. This study demonstrates that polidocanol is a safe sclerosing agent in the short and long term.

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Complications of sclerotherapy have been described previously, and we conducted the first mid-term prospective multicenter registry on side effects of sclerotherapy, which contributed to a better knowledge of complications of this technique.[1–7] The U.S. Food and Drug Administration encouraged the project of prolonging the study several more years. This survey provides long-term information on adverse events that has been unavailable until now.

Material and Methods

In this registry, patients who had received at least one polidocanol (Aétoxisclérol, Laboratoire Kreussler, Wiesbaden, Germany) injection during the observation time of the French registry, which lasted from April 2004 to April 2008, were included. The data lock point for the follow-up was end of April 2008.

The 2008 French Polidocanol Registry was established to obtain more extended long-term safety results after sclerotherapy because the observation time of the 2004 French registry ended after 8 weeks. Twelve investigators (Dr. Chleir, Neuilly sur Seine; Dr. Gillet, Bourgoinjallieu; Dr. Hamel-Desnos, Caen; Dr. Schadeck, Paris; Dr. Lausecker, Selestat; Dr. Daull Vigneron, Ecully; Dr. Chahim, Paris; Dr. Moraglia, Bordeaux; Dr. Raponsky, Selestat;

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Polidocanol is not currently licensed in the United States. This article reports its use in France and does not recommend its use in the United States.

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Dr. Stirnemann, Saverne; Dr. Marabelle, Grasse; Dr. Guex (Principal Investigator), Nice) of the 2004 French registry agreed to participate in the 2008 French Polidocanol Registry. They were asked explicitly for the following adverse events (adverse event: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product that does not necessarily have a causal relationship with this treatment; adverse reaction: any untoward and unintended response to an investigational medicinal product related to any dose administered (Directive 2001/20/EC of the European parliament and of the council, April 4, 2001)): muscular vein thrombosis, allergic reaction, anaphylactic shock, paresthesias, cutaneous necrosis, vaso-vagal fainting, visual disturbances, headache (on treatment day), and nausea and vomiting (on treatment day). Other symptoms could be included in a free text field.

Patients of the 2004 survey were first identified through investigators' data; then their files were analyzed. No Institutional Review Board or Ethics Committee approval was necessary because physicians documented their normal daily practice. Registry forms were filled out according to the patient's, chart, patients were asked to come back, or the investigators interviewed them over the telephone. For every adverse event, the physician clearly stated the relationship to the sclerotherapy treatment as excluded, unlikely, or likely, taking into account the onset of the adverse event. The registry forms were collected, and data were entered into the SAS database (SAS Institute, Inc., Cary, NC). Double data entry was performed for all data. After a query process and data reconciliation, the data base was locked, and data were evaluated. Data were analyzed using SAS software in the Department of Epidemiology and Biostatistics of the Medical University of Dijon (France).

Results

Between April 2004 and April 2008, 1,605 patients who had received at least one polidocanol injection were surveyed. A total of 3,357 patient years were covered.

Within the surveillance time of approximately 4 years, these 1,605 patients were treated in 6,444 treatment sessions. In 6,284 sessions, only polidocanol was used; in 160 sessions, other sclerosants (chromated glycerin or sodium tetradecyl sulfate) were administered alone or in combination with polidocanol. In this new registry, the focus was on adverse reactions related to polidocanol (adverse event relatedness "likely"). Therefore, only patients who received at least one polidocanol treatment were analyzed and reported (Figure 1).

In some patients who had received polidocanol, a few single sessions were performed exclusively with other sclerosants. In these cases, it could be clearly excluded that polidocanol caused the adverse events. The adverse events that were noticed in these "non-polidocanol sessions" were two visual disturbances after administration of sodium tetradecyl sulfate as foam, one superficial thrombophlebitis after therapy with liquid sodium tetradecyl sulfate, and one muscular vein thrombosis after administration of chromated glycerin. The relationship between each event and the treatment was likely in all cases. In no case did any adverse event occur after a treatment in which several different sclerosants were given (Table 1).

Most of the sessions were performed with sclerosants in foamed formulation ($n = 4,403$); the rest ($n = 2,041$) was performed with liquid sclerosants. This ratio (foam administration:liquid administration = 2.15:1) has to be taken into account when comparing the adverse reactions of liquid and foamed polidocanol.

The main calibers being treated during the observation period in patients having received at least one polidocanol injection were C1 varicose veins (70.7%), with 32.5% reticular veins and 38.2% spider veins. This was followed by great saphenous vein trunk or junction (14.8%), main tributaries

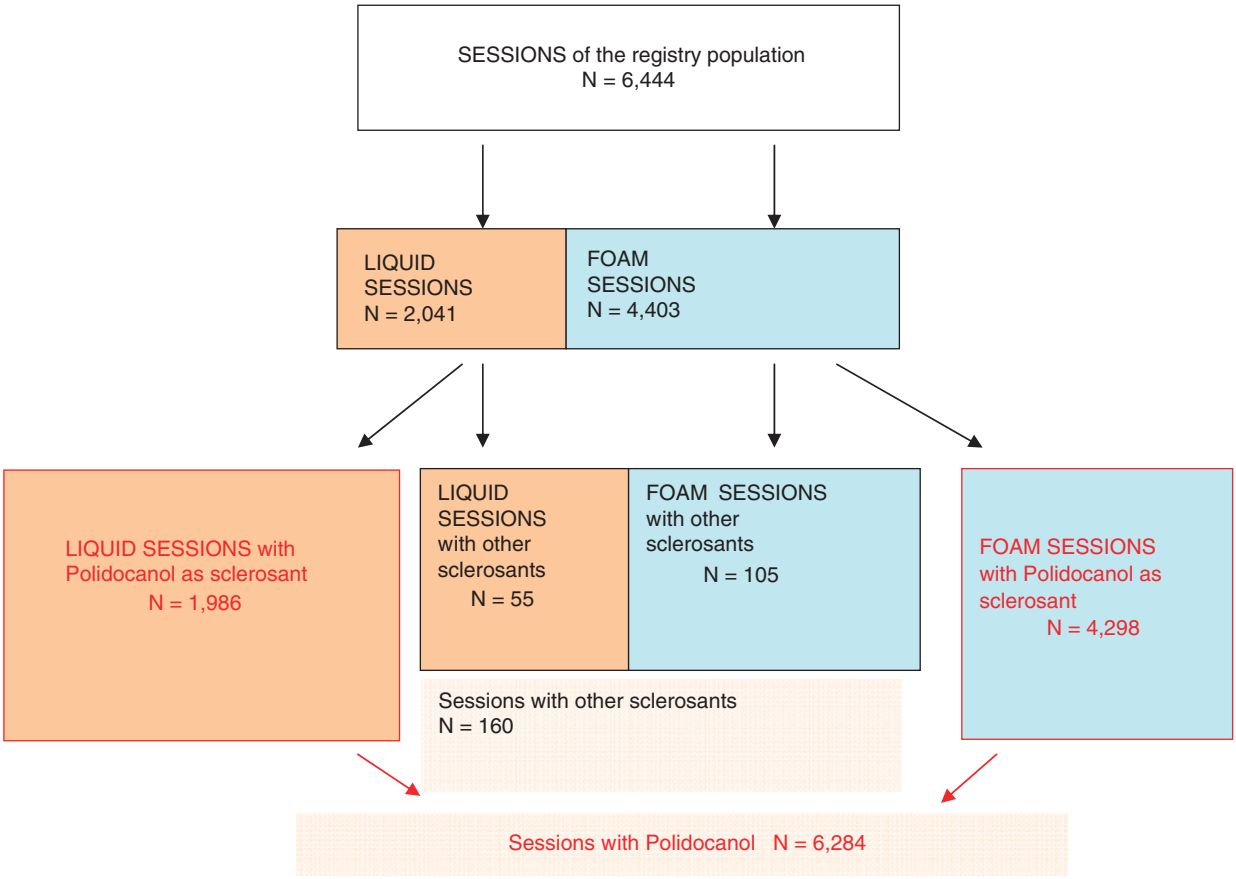

Figure 1. Numbers of sclerotherapy sessions using liquid, foam, polidocanol, and other sclerosants.

(11.3%), and small varices or nonsaphenous (9.8%) (Table 2).

Adverse Events

In 54 patients of the registry population, 68 adverse events were observed. These adverse events occurred during or after 58 sclerotherapy sessions with all kind of sclerosants (Figure 2).

Adverse Reactions

Thirty-seven patients (total of 51 sessions) showed an adverse event that could be attributed to a treatment session with polidocanol. These 51 events were defined as adverse drug reactions that were likely related to polidocanol. The global rate of incidence of averse events related to polidocanol of the registry is 0.8% (per session) and 0.02 per patient year (Table 1).

Further analysis of these events has shown that an injection with polidocanol foam caused 46 and that an injection with polidocanol liquid caused five (Table 3).

Adverse reactions after administration of polidocanol liquid:

The five reactions observed after injection with polidocanol liquid were one cramp, two inflammatory reactions, one pigmentation, and one visual disturbance. The total rate of adverse events with liquid polidocanol was 0.25%.

Adverse reactions after administration of polidocanol foam:

TABLE 1. Listings of All Adverse Events with Relatedness Likely

Sex	*Vein Type*	*Drug Used*	*Type of Treatment*	*Concentration*	*Volume*	*Adverse Event Relationship Likely*	*Onset*	*Adverse Events per Session, n*	*Adverse Events per Patient, n*
Female	Spider veins	Polidocanol	Liquid	0.25	2.5	Pigmentation	Delayed	1	1
Female	Spider veins	Chromated glycerin	Liquid	0.75	1.5	Muscular vein thrombosis	Medium	1	1
Female	Small varices or nonsaphenous	Polidocanol	Foam	0.9	2.5	Vasovagal fainting	Immediate	1	1
Female	Small varices or nonsaphenous	Polidocanol	Foam	0.5	2	Visual disturbances	Immediate	1	1
Female	Small varices or nonsaphenous	Polidocanol	Liquid	0.5	1	Cramps	Immediate	1	1
Female	Main tributaries	Polidocanol	Foam	0.9	3	Vasovagal fainting	Immediate	2	2
						Visual disturbances	Immediate		
Female	Perforating veins	Polidocanol	Liquid	3	1	Inflammatory reaction	Medium	1	1
Female	Small saphenous vein trunk or junction	Polidocanol	Foam	3	2	Inflammatory reaction	Medium	1	1
Female	Postsurgical recurrences	Polidocanol	Liquid	3	2	Inflammatory reaction	Medium	1	2
	Reticulars	Polidocanol	Foam	0.5	2	Inflammatory reaction	Medium	1	
Female	Reticulars	Polidocanol	Foam	0.25	3	Vasovagal fainting	Immediate	1	1
Female	Reticulars	Polidocanol	Foam	0.5	3	Muscular vein thrombosis	Medium	1	1
	Great saphenous vein trunk or junction	Polidocanol	Foam	1	2				
Male	Great saphenous vein trunk or junction	Polidocanol	Foam	2	3	Deep vein thrombosis	Medium	1	1
	Small saphenous vein trunk or junction	Polidocanol	Foam	2	3				
Female	Postsurgical recurrences	Polidocanol	Foam	2	3	Chemically induced phlebitis	Medium	1	1

Female	Great saphenous vein trunk or junction	Polidocanol	Foam	2	5	Visual disturbances	Immediate	1	1
Female	Main tributaries	Polidocanol	Foam	0.5	3	Vasovagal fainting	Immediate	1	1
Female	Main tributaries	Polidocanol	Foam	1	2	Muscular vein thrombosis	Delayed	1	1
	Perforating veins	Polidocanol	Foam	2	1.5				
	Postsurgical recurrences	Polidocanol	Foam	2	1.5				
Female	Postsurgical recurrences	Polidocanol	Foam	0.5	5	Muscular vein thrombosis	Medium	1	1
Female	Postsurgical recurrences	Sotradec	Foam	3	8	Visual disturbances	Immediate	1	1
Female	Great saphenous vein trunk or junction	Sotradec	Foam	3	3	Superficial thrombophlebitis	Medium	1	1
Female	Spider veins	Polidocanol	Foam	0.25	3	Headache (on treatment day)		1	1
Female	Postsurgical recurrences	Polidocanol	Foam	0.5	2	Headache (on treatment day)		1	1
Female	Great saphenous vein trunk or junction	Polidocanol	Foam	1	3	Re-entry perforator thrombosis	Immediate	1	1
Female	Spider veins	Polidocanol	Foam	0.25	3	Visual disturbances	Immediate	1	3
	Spider veins	Polidocanol	Foam	0.25	3	Visual disturbances	Immediate	1	
	Spider veins	Polidocanol	Foam	0.25	2.5	Visual disturbances	Immediate	1	
Male	Small saphenous vein trunk or junction	Polidocanol	Foam	2.5	5.5	Muscular vein thrombosis	Immediate	1	1
Female	Reticulars	Polidocanol	Foam	0.5	3	Muscular vein thrombosis	Medium	1	1
Female	Reticulars	Polidocanol	Foam	0.25	3	Visual disturbances	Immediate	1	1
	Small saphenous vein trunk or junction	Polidocanol	Foam	1	2				

TABLE 1. Continued

Sex	*Vein Type*	*Drug Used*	*Type of Treatment*	*Concentration*	*Volume*	*Adverse Event Relationship Likely*	*Onset*	*Adverse Events per Session, n*	*Adverse Events per Patient, n*
Female	Spider veins	Polidocanol	Foam	0.25	3	Visual disturbances Nausea, vomiting (on treatment day)	Immediate	2	3
	Spider veins	Polidocanol	Foam	0.25	1.5	Visual disturbances	Immediate	1	
Female	Small saphenous vein trunk or junction	Polidocanol	Foam	1.5	4.5	Muscular vein thrombosis	Medium	1	1
Female	Reticulars	Polidocanol	Foam	2	2.5	Vasovagal fainting	Immediate	1	1
Female	Great saphenous vein trunk or junction	Polidocanol	Foam	2	6	Nausea, vomiting (on treatment day)		1	1
Female	Small saphenous vein trunk or junction	Polidocanol	Foam	2	2	Visual disturbances Headache (on treatment day)	Immediate	2	2
Female	Postsurgical recurrences	Sotradec	Foam	0.2	5	Visual disturbances	Immediate	1	1
Female	Small varices or nonsaphenous	Polidocanol	Foam	0.25	4	Visual disturbances Headache (on treatment day)	Immediate	2	2
Female	Spider veins	Polidocanol	Foam	0.25	2.5	Vasovagal fainting Chest oppression Shortness of breath	Immediate Immediate Immediate	3	3
Female	Spider veins	Polidocanol	Liquid	0.33	2	Visual disturbances	Immediate	1	1

Female	Great saphenous vein trunk or junction	Polidocanol	Foam	2	1	Headache (on treatment day) Nausea, vomiting (on treatment day)	2	2	
Female	Spider veins	Polidocanol	Foam	0.25	2.5	Visual disturbances Headache (on treatment day)	Immediate	2	2
Female	Spider veins	Polidocanol	Foam	0.33	2.5	Muscular vein thrombosis	Medium	1	1
Female	Spider veins	Polidocanol	Foam	0.33	2.5	Allergic reaction Headache (on treatment day)	Medium	2	2
Female	Main tributaries	Polidocanol	Foam	2	1.5	Muscular vein thrombosis	Delayed	1	1
Female	Small saphenous vein trunk or junction	Polidocanol	Foam	0.5	4	Paresthesias Visual disturbances	Immediate Immediate	2	2

Adverse events are listed case by case on a per-patient basis. In the rare case that sclerosants other than polidocanol were given exclusively during a session, this is marked in grey.

Most common adverse reactions directly related to polidocanol foam were 13 visual disturbances. Only one such event could be seen after treatment with the liquid. There were seven cases of headaches (including migraines), and eight muscular vein thrombosis were noticed with polidocanol foam.

One deep vein thrombosis (DVT) occurred at mid-term after administration of polidocanol foam. According to the physician's report, the patient had thrombophilia (heterozygote Factor V Leiden). The patient's medical history revealed a DVT with an onset long before sclerotherapy with polidocanol was performed. Even though the patient had been advised to take prescribed anticoagulants, the medication had been stopped. Sclerotherapy was performed during this period. The physician stated that the DVT was likely related to sclerotherapy with polidocanol, but it is more likely that the event was a recurrence of the former DVT and inappropriate termination of anticoagulant therapy. The total incidence of adverse events with foamed polidocanol was 1.07%.

Duration of Follow-Up and Onset of Adverse Reactions

Almost three-quarters (71.8%) of the patients were followed up for at least 12 months, and 59.0% were followed up for 24 months (Table 4).

During this observation time, most adverse events occurred on the treatment day or directly afterwards, so in 51.0% of all adverse events, physicians declared the onset to be immediate (same day) and 74.5% immediate or medium delay (<4 weeks) (Figures 3 and 4).

Discussion

Adverse reactions published in this study and those presented in our previous survey (French Polidocanol Registry 2004) differ slightly because not all investigators of the French Registry 2004

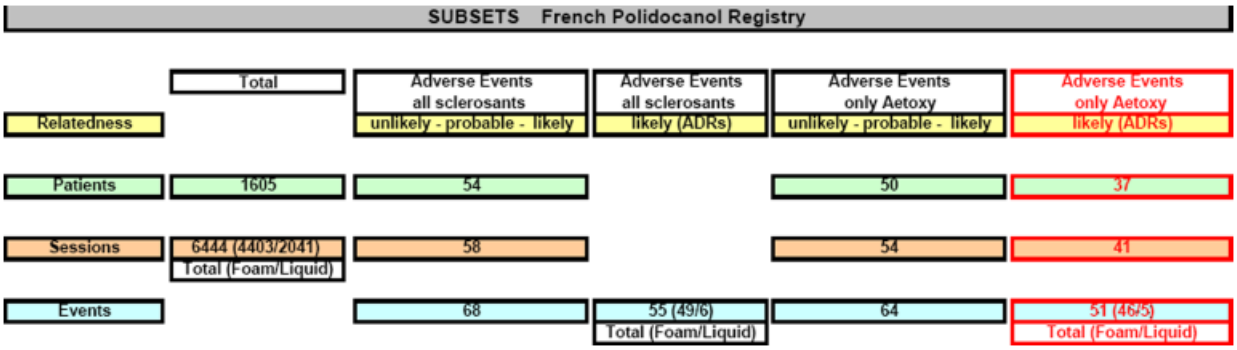

Figure 2. Subsets of patients, sessions, and events.

participated in this follow-up register, and only patients who had received at least one polidocanol injection in the 2004 French registry were included in this current registry.[6] Some complications were lost from the registry because patients were not included, although roughly the same side effects were observed, with similar incidence. The nature and frequency of complications described in the literature are similar to our findings.[8] It should be taken into account that, being a registry and not an interventional study, duplex scanning was only performed in accordance with the daily practice (in case of signs or symptoms of adverse events) or to check the efficacy of sclerotherapy.

TABLE 2. Sessions (Liquid and Foamed Sclerosants) for Each Vein Type (Only Subsets of Patients Receiving 1 Injection with Polidocanol)

Type of Vein	n *(%)*
Reticular veins	2,096 (32.5)
Spider veins	2,461 (38.2)
Great saphenous vein trunk or junction	951 (14.8)
Small saphenous vein trunk or junction	291 (4.5)
Main tributaries	727 (11.3)
Small varices or nonsaphenous	629 (9.8)
Perforating veins	157 (2.4)
Postsurgical recurrences	668 (10.4)

Different vein types could be treated in one session.

Liquid sclerotherapy has a lower incidence of side effects than foam sclerotherapy (Tables 1 and 2), but it does not have the same efficacy and mostly not the same indications. From our experience, we recommend the use of liquid polidocanol for treatment of spider, reticular, and small varicose veins whose severity and potential complications are limited. Conversely, polidocanol foam sclerotherapy under

TABLE 3. Adverse Reactions—Likely Related to Aétoxiscléro l—in Relation to Type of Treatment (Foam or Liquid)

	n *(%)*	
Adverse Reactions	*Foam*	*Liquid*
Allergic reaction	1 (2.2)	
Cramps		1 (20.0)
Deep vein thrombosis	1 (2.2)	
Shortness of breath	1 (2.2)	
Headache (on treatment day)	7 (15.2)	
Inflammatory reaction	2 (4.3)	2 (40.0)
Muscular vein thrombosis	8 (17.4)	
Nausea, vomiting (on treatment day)	3 (6.5)	
Chest tightness	1 (2.2)	
Paresthesia	1 (2.2)	
Pigmentation		1 (20.0)
Re-entry perforator thrombosis	1 (2.2)	
Vasovagal fainting	6 (13.0)	
Superficial phlebitis	1 (2.2)	
Visual disturbances	13 (28.3)	1 (20.0)
Total	46 (100.0)	5 (100.0)

duplex guidance is generally more appropriate for the treatment of large varicose veins, because severe venous disorders may cause discomfort, restriction of activities, and serious complications and therefore allow the use of a stronger treatment. We suggest limiting the use of foamed sclerosant for reticular and spider veins to selected cases resisting the liquid form.[9]

Current evidence does not demonstrate the superiority of foam in the treatment of spider and reticular veins.[10] Studies and registries show more side effects with foam, such as microthrombus and discoloration and visual troubles.[7] Therefore, it is suggested that foam not be the primary sclerosant of spider and reticular veins.[11]

Even if they were scarce in this registry, we observed two main types of adverse reactions after foam treatment: thrombotic complications and neurosensorial complications, mostly visual troubles.

We described specifically muscular venous thrombosis; other teams call them deep venous thrombosis, mostly anatomical and functional but also because of their decreased potential for complications such as pulmonary emboli and posthrombotic syndrome. Muscular venous thromboses are deep thromboses of less severity,[12] although they can extend into deep venous thrombosis, and they must be treated appropriately as soon as possible. Recommendations exist, and we suggest the same management as for DVT (elastic compression, low-molecular-weight heparin for 7–10 days, and up to 3 months of oral anticoagulation).[13]

To some extent, thrombotic adverse reactions occur with sclerotherapy but remain scarce and are benign in the extreme majority of cases.

Neurosensorial adverse reactions seem to be mostly associated with the use of foam (Tables 1 and 3). The origin of these complications remains unclear. The responsibility of a patent foramen ovale has been indicated[14] but is not the only possible explanation, and other authors suggest endothelial mediators circulation after endothelium chemical destruction.[15]

No stroke or transient ischemic attack was observed in our registry. Other adverse reactions were non-

TABLE 4. Duration of Follow-Up Per Patient (in Months)

Duration of Follow-Up, Months	*Subjects, (%)*	*12 Months of Follow-Up*	*24 Months of Follow-Up*
0–1	102 (6.8)		
1–2	68 (4.6)		
2–3	56 (3.7)		
3–4	37 (2.5)		
4–5	39 (2.6)		
5–6	21 (1.4)		
6–12	97 (6.5)		
12–18	115 (7.7)	71.8%	
18–24	76 (5.1)		
24-32	130 (8.7)		59.0%
32–38	176 (11.8)		
38–44	226 (15.1)		
44	349 (23.4)		
Total	1,492 (100.0)		

N	*Mean*	*Standard Deviation*	*Median*	*Minimum*	*Maximum*
Missing data: 113 1,492	26.93	17.30	32.57	0	59.34

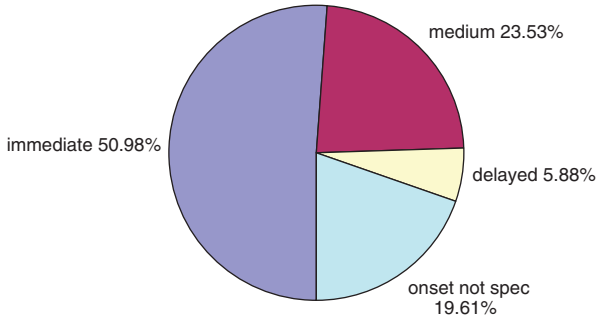

Figure 3. Onset of adverse reactions after treatment with liquid and foamed polidocanol (subset of patients having received at least one injection with polidocanol).

specific or scarce. Allergy might exist, but because of its low incidence, its demonstration would require an enormous registry with high patient numbers.

In the recently presented CESMOUS study, in which all patients underwent full duplex scanning after foam sclerotherapy, five symptomatic venous thromboses (4 muscular, 1 distal), five asymptomatic venous thromboses (3 deep distal, 2 common femoral veins), and one unlikely pulmonary embolism without evidence of DVT, were found after treatment of 1,000 saphenous veins with foam.[13]

In our registry, no significant neurologic reaction has been observed but some are described in the literature[16] (plus one benign transient ischemic attack in the CESMOUS study, previously cited).[13] The safety of polidocanol foam has also been shown in the ESAF Study, in which polidocanol foam and liquid were applied to the great saphenous vein. Better than liquid, foam has also proven to be equally safe.[16]

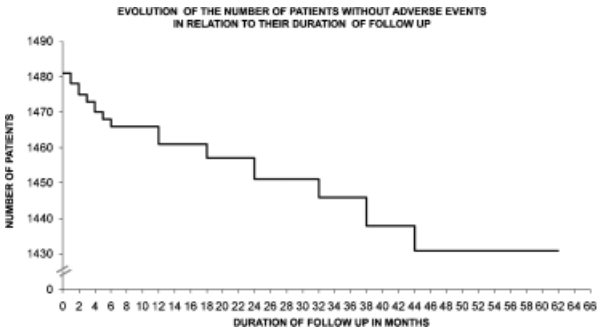

Figure 4. Onset of adverse events.

Conclusion

Sclerotherapy with polidocanol is safe, especially in the long term. It is acknowledged as the criterion standard for most types of varicose veins, and ultrasound-guided foam sclerotherapy is a reference method in the treatment of incompetent saphenous trunks. The use of liquid, with an incidence of side effects lower than 0.4%, perfectly fits for the treatment of benign lesions such as small varices, reticular veins, or telangiectasias, whereas foamed polidocanol injected under ultrasound guidance used in the treatment of large varicose veins presents fewer side effects than surgery, with which it now competes.

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