Original Article

Role of virus inactivated cryoprecipitate in the treatment of bleeding disorders

Jean-Claude Faber

Association Luxembourgeoise des Hémophiles, Luxembourg, Luxembourg

Correspondence to: Dr. Jean-Claude Faber. 33, Rue Albert Ier, L-1117 Luxembourg, Luxembourg. Email: jean.claude.faber@numericable.lu.

Background: Treatment of patients with bleeding disorders has significantly improved in terms of quality, safety and efficacy. Despite impressive medical and pharmaceutical progress, serious problems continue to exist with the treatment of these patients: (I) in developing countries, treatment of patients with bleeding disorders is inadequate. In total, 75% to 80% of all hemophiliacs in the world have no access to any form of effective treatment, for different reasons: needed blood products are unavailable, inaccessible and/or unaffordable. Even more striking, this situation has hardly changed over the past 20 to 30 years and remains catastrophic and unacceptable in resource limited countries; (II) although many complications resulting from hemophilia can be avoided nowadays, one major side-effect continues to exist with the use of clotting factor concentrates in hemophilia patients: the formation of inhibitors, neutralizing alloantibodies against injected coagulation factors. This potentially life-threatening complication arises frequently in previously untreated patients with severe hemophilia A (according to a recent study, in at least 25% to 35%) and poses them at serious risk.

Methods: Recently, significant developments have occurred with the potential to change the situation: blood systems (including blood centers and services) in developing countries have in general tangibly improved and novel technologies for viral inactivation (VI) of blood components are now available and marketed (using amotosalen, riboflavin, solvent-detergent, etc.).

Results: In a few countries, local preparation of virus inactivated cryoprecipitate (Cryo-VI) is used, like in Egypt where about 1/3 of the national factor VIII (FVIII) consumption is covered by Cryo-VI, and it has proven to be a safe and effective therapeutic for patients with bleeding disorders, at an affordable cost. If rolled out into developing countries, it is foreseeable that supply, availability, accessibility and affordability of therapeutic hemostatic products will sensibly improve. At the same time, inhibitor occurrence can be drastically lowered as it is well known from historical data and long-term clinical experience that only around 5% of hemophilia A patients treated with cryo develop an inhibitor. Despite these promising facts, introduction and use of Cryo-VI remains limited in the world. There are many different obstacles for the use of this simple and inexpensive technology.

Conclusions: A worldwide coordinated movement involving all stakeholders is needed to facilitate introduction, implementation and maintenance of local preparation of Cryo-VI. Cryo-VI has undoubtedly the potential to improve the existing situation by alleviating shortage or absence of needed hemostatic products in low Human Development Index (l-HDI) and by lowering the incidence of inhibitors in newly treated hemophilia A patients.

Keywords: Hemophilia; clotting factor concentrates (CFC); cryoprecipitate (cryo); viral inactivation (VI); virus inactivated cryoprecipitate (Cryo-VI); solvent-detergent (SD); inhibitors

Received: 24 October 2017; Accepted: 22 November 2017; Published: 07 March 2018.

doi: 10.21037/aob.2018.01.04

View this article at: http://dx.doi.org/10.21037/aob.2018.01.04

Introduction

In the past 2 or 3 decades, treatment of patients with bleeding disorders has improved significantly and people with hemophilia A or B, von Willebrand disease, fibrinogen abnormalities and other hematological disorders affecting plasma coagulation (called hereafter "hemophiliacs") have benefited greatly from medical and pharmaceutical progress. Most of these disorders rely on substitution therapy of the clotting factor which is absent or lowered or dysfunctional in the patient by injecting products that have continuously improved, above all in safety and especially in avoiding transmissible viral infections.

In almost all countries of the developed world comprehensive health care systems exist which guarantee to their populations availability, accessibility and affordability of safe and effective medicinal products.

Unfortunately, this is not the case in developing countries [with low Human Development Index (l-HDI)]. According to World Federation of Hemophilia (WFH), the situation of patients with bleeding disorders in l-HDI is unsatisfactory: at least, 75% to 80% of patients with hemophilia have no access to any form of appropriate treatment (1). Even more striking than this raw figure, is the fact that despite several initiatives, this unbearable situation has not changed during the past 20 to 30 years and product shortages are the daily reality for patients with bleeding disorders in l-HDI.

In addition to dramatic chronic product shortages, the actual therapeutic schemes relying mostly on clotting factor concentrates (CFC) come with a serious complication, the formation of inhibitors. The neutralising alloantibodies affect in particular patients with severe hemophilia A and are directed against injected factor VIII (FVIII). The potentially life-threatening complication renders substitution therapy unpredictable and less effective and occurs frequently in previously untreated patients (PUP) with severe hemophilia A: at least, 25% to 35% of the patients suffer this serious and potentially life-threatening adverse reaction (2). Many believe that inhibitors are triggered more often by recombinant than plasma-derived products, at least those containing von Willebrand factor (2,3), are more frequent in hemophiliacs being in "immunological storm" than on controlled prophylactic treatment, occur more often in Black populations than in Caucasians. Thus, possibly one in two hemophiliacs in Africa develops an inhibitor as these patients are often treated in "emergency-like" situations, with recombinant FVIII (rFVIII) products, donated by industry.

Recently, promising developments have occurred which offer significant potential to change the disastrous situation in therapy delivery for "hemophiliacs": blood systems (and above all, blood services, blood establishments or blood centers) in many l-HDI countries have tangibly improved and novel technologies for viral inactivation (VI) of blood components are now available and marketed [using e.g., amotosalen, riboflavin, solvent-detergent (SD) and others]. Despite these encouraging facts, the situation in hemophilia treatment has not yet changed in l-HDI countries and different barriers are obstructing relief for patients with bleeding disorders.

Methods

How to solve or alleviate existing problems?

In some developing countries, virus inactivated cryoprecipitate (Cryo-VI) is locally produced, clinically used and has proven to be a safe and effective therapeutic for patients with defined bleeding disorders, at an affordable cost. Therefore, it appears that local preparation of Cryo-VI ("Local Cryo-VI") has the potential to substantially alleviate the supply situation when CFC are not available, mostly because of limited financial resources. It should be mentioned here that not only patients with inherited bleeding disorders would benefit from "Local Cryo-VI" but also those with acquired dysfunctioning coagulation (like women suffering severe complications at child delivery and developing hypo-/afibrinogenemia, a life-threatening condition and one of the leading causes of maternal mortality in l-HDI).

Also, historical data and long-term clinical experience from the past have shown that only around 5% of the treated patients developed an inhibitor when they were treated with cryoprecipitate (cryo). It can be reasonably assumed that use of safe cryo (Cryo-VI) will lower the risk of inhibitor development in hemophilia A patients significantly and many desperate situations will be avoided in l-HDI as patients forming an inhibitor are "lost" because conventional substitution therapy has become ineffective due to neutralizing anti-FVIII and eradication of the inhibitor [through immune tolerance induction (ITI)] is out of reach there due to lack and unaffordability of specialized therapies (like bypassing agents).

What is safe cryo and how is it produced?

Cryoprecipitate (or cryo) is a component containing

the cryoglobulin fraction of plasma obtained by further processing of fresh frozen plasma prepared from hard-spun cell-free plasma and concentrated most commonly to a final volume of 10 to 20 mL. Cryo contains a major portion of the FVIII, von Willebrand factor, fibrinogen, factor XIII and fibronectin present in freshly drawn and separated plasma (4).

In the past, cryo has been used for a long time in the treatment of hemophilia A.

At present, it continues to be used widely and extensively in developing countries because in most instances no CFC are available. As cryo is used in its "native" form (e.g., untreated), like other blood components (red cells, platelets, frozen plasma), it bears the risk of acquiring transfusion transmissible infections (TTI, like HBV, HCV, HIV).

In order to eliminate the risk of TTI, cryo can undergo VI or pathogen reduction (PR) and is converted into Cryo-VI through this additional processing step. Basically, "native" cryo is mixed with a chemical compound or several chemicals, with or without illumination and at the end of production a safe product is available: Cryo-VI.

In principle, the following VI technologies can be used when preparing blood components to make them TTI-safe for patients, including those with certain bleeding disorders (5):

- SD, without any light exposure (6);
- Amotosalen (S-59), exposed to ultraviolet light (UV A) (7);
- Riboflavin (vitamin B2), with UV illumination (8).

So far, for the purpose of producing safe cryo, only one of these technologies has been fully developed, fulfilled necessary tests and studies, received required regulatory authorizations and approvals from authorities and is marketed by the manufacturer: it uses SD treatment and filtration with the medical device Cryo-SD/F® from VIPS (9).

The other PR-technologies have not yet been further developed to be applied on Cryo-VI or brought to the market by the companies, for reasons which are not known to this author. Nonetheless, the views expressed hereafter on Cryo-SD/F apply in principle also to amotosalen (Intercept® from Cerus) and riboflavin (Mirasol® from TerumoBCT).

Results

What potential does Cryo-VI hold to improve the existing unsatisfactory situation?

Cryo is a remarkable substance of human origin, containing many different important plasma proteins, some in concentrated form such as FVIII, von Willebrand factor, and fibrinogen.

With SD/F VI technology being available, a new generation of cryo can now be prepared: virus inactivated cryoprecipitate (Cryo-VI or more precisely: Cryo-SD/F), presenting the following important characteristics relating to:

Safety

As already mentioned, in many developing countries cryo may be the only product available to treat patients with bleeding disorders, like hemophilia A, von Willebrand disease and disturbances of fibrinogen. As this form of cryo is "native" or untreated whatsoever, it bears the risk of viral transmission (or TTI). Depending on the local epidemiological situation of the blood donors, this risk may be substantial (for example, when prevalence/incidence of HBV, HCV or HIV are high among them). VI techniques are very efficient in "killing" relevant viruses: for amotosalen and riboflavin through cross-linking the DNA/RNA strands and rendering viral replication impossible, for SD through disrupting the viral capsule of TTI viruses, the relevant ones being all lipid-enveloped. Based on these facts, and considering the robustness of the SD technology against lipid-enveloped viruses, and the small pool made, it is beyond reasonable doubt that Cryo-SD/F is a safe product (9,10).

Quality

Cryo-SD/F is not only a safe product but also a high quality therapeutic when prepared in the blood centers with required care and under professional conditions. It comes reproducibly with predefined specifications when it is processed according to validated procedures and in compliance with set standards. Typically, the final production bag of Cryo-SD/F derived from a pool of 30 to 35 "native" cryos contains high therapeutic doses of FVIII:C, WF R:Co and fibrinogen (11). In this regard, Cryo-SD/F may be compared to plasma-derived CFC, with Cryo-SD/F having a lower purity as compared to CFC.

In clinical trials and routine use, Cryo-SD/F has shown no relevant side-effects nor adverse reactions. Above all, no viral transmission nor any inhibitor formation have been encountered with Cryo-SD/F.

Efficacy

In clinical studies and in routine use, Cryo-SD/F has proven so far hemostatic efficacy in hemophilia A patients. It has controlled haemorrhages and prevented bleeding in

surgery, as expected (11). According to a retrospective study over several years (12), safety and efficacy of Cryo-SD/F are demonstrated based on the use of more than 10 million IU FVIII.

Availability

The preparation of "native" cryo is not a complex process and it should be part of regular activities in major blood centers in developing countries, supplying blood and blood components to hospitals. VI of "native" cryo is for most developing countries a new technology which needs to be integrated into the existing work flow as an additional step at the end of preparing blood components from whole blood. For the implementation of Cryo-SD/F, it may be advisable for developing countries to introduce VI stepwise, starting with the national blood center (NBC), possibly also with larger regional blood centers (RBC), which can initially ensure most of the supply of Cryo-VI. Later on, VI technology may be rolled out to smaller blood centers, if necessary. With such an organisation, the supply issues can be addressed in a satisfactory way, making Cryo-VI available to most diagnosed patients with bleeding disorders. How much Cryo-SD/F can be delivered at national/regional level will depend primarily on the blood/plasma collection volumes of the blood centers, on requests for this product and also on available financial means.

In the absence or chronic shortage of products suitable for treating patients with bleeding disorders, any additional source will be a major step forward: Cryo-SD/F has the potential to contribute to the goal of "Treatment for All" (WFH: "50 years of advancing Treatment for All", www.wfh.org).

Accessibility

The design of the national blood system in a developing country will determine the ease of access to Cryo-SD/F for patients with bleeding disorders. If coverage of blood/blood components is ensured across the entire territory, Cryo-VI can become accessible in hospitals all over the country. If blood/blood components are accessible only in certain areas, Cryo-VI will also be limited (for example, to big cities with large hospitals and major blood suppliers). Therefore, it can be assumed that accessibility by patients to "classic" blood components (like red blood cells, platelets and fresh frozen plasma) will also condition directly access to Cryo-VI. In any case, adding Cryo-SD/F to the product portfolio of large blood establishments in a developing country will undoubtedly increase access to hemostatic products for the patients with bleeding disorders (if diagnosed at all, which is yet another problem and challenge).

Affordability

All blood products and blood components come with a cost, whether offered by voluntary non-remunerated blood donors or given by paid donors. All activities needed to achieve high levels of safety and quality in therapeutic products are causing expenses. Depending on the product, there is important variation in cost and price.

This is particularly true for products used for the treatment of patients with bleeding disorders. For hemophilia A, the price for industrially-manufactured CFC varies significantly from one country to another: 1 IU of FVIII concentrate may cost as little as 0.25 USD but also as much as 1 USD or even more [personal communications in developing countries (2010–2017)], depending on whether it is a plasma-derived or a recombinant product, on the country of purchase, on the volume of product bought, whether there are public tenders or not, whether the manufacturer sells his product directly or through a local dealer, on customs taxes and related expense, etc.

In general, it is not wrong to say that developing countries are not privileged by the manufacturers when it comes to the price to pay for CFC. In contrast to CFC, the costs for Cryo-SD/F are relatively low: there is a small expense for preparing "native" cryo, the cost for VI being added on top, in case of VIPS medical device for Cryo-SD/F®, some 0.07 USD per IU FVIII (12). The low price for Cryo-VI (as compared to CFC) is explained by the fact that "native" cryo can be produced locally in the blood center, then undergo VI in the blood establishment where premises, equipment and staff are anyway in place for routine preparation of blood components from whole blood donations. It is indisputable that preparation of Cryo-SD/F is a cost-effective intervention and is in financial reach of many developing countries.

This becomes even more evident when looking at the overall financial burden relating to hemophilia treatment. The final bill for the society in a given country (developed or developing) has basically two components:

- For regular treatment of hemophiliacs;
- For the treatment of hemophilia patients with an inhibitor.

For both categories of patients, mainly CFC are used around the world and most of them are purchased from commercial companies.

For patients without an inhibitor, different therapeutic

schemes are used: the range is very large and stretches from "on-demand" with low doses (even in critical clinical situations) to "prophylaxis" or prevention with high doses and high frequency (to avoid any bleeding risk).

For patients with an inhibitor, bypassing agents are injected and/or ITI is tried to eradicate the neutralizing antibody. For ITI, the treatment is long and is consuming colossal amounts of CFC, causing in average a huge expense per patient. But not only costs are relevant in the context of inhibitors, ITI is stressing and potentially traumatizing for the patient and his family. ITI also has a significant impact on availability of hemostatic products because CFC used for ITI create high demand, high prices and even shortage (at least, relative for the developing world).

With Cryo-SD/F, the costs for production are relatively low and the costs for eradication of formed inhibitors will be only a fraction of those subsequent to the use of CFC, the incidence of inhibitors being significantly lower with Cryo-VI.

Sustainability

As already mentioned, Cryo-SD/F can be easily prepared by local blood centers (equipped and staffed anyway to produce "classic" blood components). As whole blood and blood components are pivotal for any health care system and are considered "essential medicines" in WHO's List of Essential Medicines (13), the activities of blood centers/blood services are of paramount importance in all jurisdictions, including developing countries. In most l-HDI, the basic activities in blood centers are granted financial support from the governments with some priority. Adding Cryo-SD/F to already available blood components will not come with an unbearable financial burden, especially if put into the context of clinical benefits achieved. Therefore, it may be expected in l-HDI that the additional expense for VI (basically caused to purchase medical devices necessary for VI treatment) is not endangering the existing and sustained blood sector.

Equity and justice

The recently revised Code of Ethics of the International Society of Blood Transfusion (ISBT) calls, inter alia, for justice and equity in the context of blood transfusion. One might include under the umbrella of these principles not only patients, but also donors, whether giving blood or plasma (14). Strikingly, 80% of all plasma-derived CFC are manufactured from plasma donations originating from paid donors, mainly in the US. This may be considered as potentially risky but without any doubt it is an unethical constellation. Whether introduction of Cryo-SD/F will change the existing imbalance is not yet known, depending on but the possibility to virus inactivate cryo may at least open the ethical debate (from the point of view of FVIII concentrates).

Independency

Also relating to the principles of equity and justice is the risk of reliance on one single country producing the vast majority of source material (15) for the manufacturing of plasma-derived CFC and the dependency of other countries resulting from this imbalance. Cryo-SD/F has the capability to "release" parts of a patient population (those with hemophilia A) from this dependency on a few international commercial companies by opening supply channels which are under national or regional control.

Inhibitor formation

As largely known, the most serious complication with actual hemophilia A treatment is the formation of inhibitors or neutralising alloantibodies which are directed against injected FVIII. It is a potentially life-threatening complication (e.g., intracranial and cerebral hemorrhages), rendering substitution therapy unpredictable and less effective and occurring in PUP with severe hemophilia A much more frequently than initially admitted.

The inhibitor problematic has been underestimated and "under-prioritized" for a long time and is affecting especially developing countries due to unfavorable constellations there.

In recently published studies (2,3), the reported incidence was 17% and 25% for plasma-derived CFC, 33% and 35% for recombinant CFC.

The SIPPET study (Survey of Inhibitors in Plasma-Product Exposed Toddlers) (2) has stimulated the discussion about this threatening problem.

The very recent FranceCoag study (3) has basically confirmed the findings of the SIPPET study.

In the meanwhile, many believe that recombinant CFC are more likely to trigger an inhibitor than plasma-derived CFC. In the context of humanitarian aid, it needs to be well understood that the majority of products donated by industry for the resource limited countries are recombinant CFC.

Also, inhibitors are more frequently formed in hemophiliacs being in "immunological storm" than on controlled prophylactic treatment, more often in Black populations than in Caucasians.

Table 1 Comparison of products most frequently used in hemophilia treatment: pros and cons as well as drawbacks

Type of product	Pros/cons		
	Advantages	Disadvantages	Problems & threats
Cryo	Feasible when plasma from whole blood donations available; inexpensive; effective; few inhibitors (ca. 5%)	Frozen storage; less comfortable for home treatment	Risk of TTI
CCF	Safe & effective; comfortable handling; when donated: free of charge	When purchased: high costs	High inhibitor formation (25–35%) in PUP with severe hemophilia A; when donated: dependency from donors
Cryo-VI	Feasible when plasma from whole blood donations available; safe& effective; easy to prepare; affordable; few inhibitors	Frozen storage; less comfortable for home treatment	–

Cryo, native, untreated cryoprecipitate; CCF, clotting factor concentrates; Cryo-VI, virus inactivated cryoprecipitate; TTI, transfusion transmissible infections; PUP, previously untreated patients.

Adding all negative factors, it may well be that 1 in 2 treated patients in Africa develops an inhibitor as hemophiliacs are often treated in "emergency-like" situations, with rFVIII products donated by industry. As a result, patients in l-HDI forming an inhibitor are most likely to be "lost" as no bypassing agents are available nor can they undergo ITI to try to eliminate the inhibitor.

For cryo, historical data and past clinical experience show that the inhibitor appearance is around 5% (16). As Cryo-SD/F has basically the same physiological and biochemical characteristics as "native" cryo, it can be reasonably assumed that a similar low level of inhibitors will occur with Cryo-VI.

Including Cryo-SD/F in the initial treatment of PUP with severe hemophilia A would very likely reduce the incidence of inhibitor appearance. The Global Initiative suggests to look into the adequacy to use Cryo-SD/F for these patients in developing countries for the first 10–20 treatment days, to test for inhibitors and, if negative, to switch onto CFC, if desired and available. Such an approach would not mean discrediting CFC, it would rather have a protective effect against FVIII alloantibody formation before switching eventually to CFC.

Considering all different important aspects listed here above, there should be no doubt that Cryo-SD/F has some advantages over CFC (see *Table 1*). Above all, it is able to alleviate existing supply issues in developing countries and to lower the incidence of inhibitors.

What are the barriers for the breakthrough of Cryo-VI in developing countries?

Different technologies for VI of plasma and platelets have been developed in the late 1990s but have not yet been brought to "market maturity" for cryo. Since 2010, a medical device is commercialized by VIPS to produce safe cryo with its medical device Cryo-SD/F®.

Taking into account the benefits of Cryo-SD/F in terms of safety, quality, availability, accessibility, affordability and low inhibitor formation, it is rather striking and somewhat difficult to understand why Cryo-SD/F is not successfully implemented at large scale in developing countries to fill the existing gaps in treatment of patients with bleeding disorders.

Discussion

Hereafter will be discussed several issues obstructing implementation of Cryo-SD/F in l-HDI:

International guidelines on treatment of bleeding disorders

Although several guidelines mention cryo as a therapeutic product for the treatment of "hemophiliacs", not a single guidance document is mentioning or recommending Cryo-VI. Recommendations given by WFH, World Health Organisation (WHO), EDQM/CofE (European Directorate for Quality in Medicines & Health Care of the Council of Europe), ISBT (International Society of Blood Transfusion), ISTH (International Society of Thrombosis and Haemostasis), AABB (American Association of Blood Banks), EBA (European Blood Alliance), etc. are either incomplete or outdated. These guidelines only mention "native" cryo as a possible hemophilia treatment option in the absence of other treatment means (e.g., CFC), with

strong warnings about existing risks of acquiring TTI.

The most prominent clinical guidelines come from WFH (17) and they are strongly promoting CFC (recombinant or plasma-derived), which are out of financial reach for most of resource-limited countries. These guidelines on the management of hemophilia date back to 2012, with minor modifications in 2013 and Cryo-VI is not even mentioned nor recommended as a safe alternative in case CFC are not available.

ISBT has recently focused on "plasma for fractionation and virus inactivated cryoprecipitate". Its WP on global blood safety has finalized a long list of recommendations on these subjects, which are of high relevance for developing countries, and has forwarded the set of recommendations to the ISBT board of directors for further action.

The Council of Europe (EDQM, European Directorate for Quality of Medicines) is covering cryo in its 18th edition of the Guide Rec. [95] 15 (4), but has not yet dealt with Cryo-VI in a dedicated monograph: this is planned for the coming 19th edition of its "Guide to the preparation, use and quality assurance of blood components".

Initiatives by international governmental organisations

WHO and its Blood Safety Programme in Geneva are recognizing the importance of cryo for patients with bleeding disorders, but so far have not yet undertaken specific initiatives to foster Cryo-VI. The leading international organisation in health matters has started recently to consider concrete steps for advocacy and promotion of safe cryo (Cryo-VI).

Initiatives by patient organisations

WFH has been set up as a patient organisation, federating national patient associations defending the interests of "hemophiliacs". WFH aspires to "Treatment for All" and has to recognize that the worldwide supply situation is highly unsatisfactory and that it has not really changed in the past 2 or 3 decades. WFH's efforts to achieve the goal of "Treatment for All" are mainly concentrated on CFC and focused on "advocacy with governments" to pay for these expensive medicines and on "product donations" by industry (1).

WFH's guidelines are widely used during advocacy campaigns with governments, health agencies and social security to get their financial commitment for hemophilia treatment and, as Cryo-VI is not mentioned in the guidelines, CFC appear as the sole therapeutic products.

Following guidance given by WFH, most hemophilia associations (being WFH national member organisations) follow this guidance and strive for CFC which is understandable, but not very pragmatic nor successful in developing countries.

Clinical studies and feasibility assessments

It is difficult to understand why commercial companies are not fully exploring and exploiting the VI technologies for which they detain intellectual rights: amotosalen and riboflavin (both with exposure to UV light) could open new markets, but astonishingly no visible efforts are undertaken to expand the application of these VI technologies from plasma and platelets to cryo.

Of course, investment would be needed to perform validation studies and clinical trials, but it should be rather limited as the main part of the regulatory work has already been done when bringing VI technologies to the market for platelets and plasma. To the knowledge of the author of this article, so far, not one single comprehensive feasibility assessment has been undertaken at a national level for the implementation and maintenance of Cryo-VI.

Expectations of patients and treating physicians

It is very well understandable that all patients desire the best possible treatment. This is similar or identical for patients with hemophilia and their requests for maximal therapy are perfectly legitimate. If in a given resource limited country, CFC are not available or not in sufficient amounts to treat all those diagnosed with hemophilia, patients should receive fair information and comprehensive education about the situation to take an informed decision about the available options: in the absence of CFC, they can decide to be treated with safe cryo (Cryo-SD/F) or not to be treated at all (or to rely just on RICE: rest, ice, compression and extension). Very often, objective and unbiased information about treatment alternatives to CFC is not given correctly or not at all and therefore it cannot be blamed on hemophiliacs to strive for CFC and only for CFC. Unfortunately, circumstances in many countries/regions do not permit access to CFC, but Cryo-VI can be an excellent alternative.

It should also be the responsibility of national patient organisations to lobby for temporary solutions (e.g., Cryo-SD/F) as long as CFC are not available—unrealistic

promises and wrong hopes are not helpful for bleeding patients in resource limited countries.

Concerning treating/prescribing physicians of hemophilia patients, very similar considerations are applicable: correct information and clear messages are urgently needed, especially in developing countries, to avoid disappointment/frustration for the patients. Cryo-SD/F allows for an effective and safe form of substitution treatment which may be not the maximum, but an optimum in a given country situation, possibly limited to a time period when resources allocated to health care are constrained. It is undisputable that use of Cryo-SD/F can avoid tremendous suffering and unnecessary death of patients with bleeding disorders.

Reputation and perception

Cryo has been successfully used in the treatment of bleeding disorders for several decades. With the advent of the HIV pandemic and numerous transmissions of the virus to hemophiliacs in the 1980s, cryo was tainted with a negative image with patients, patient organisations, treating physicians, competent authorities, etc.

It needs to be mentioned here that most of the HIV infections did not occur through cryo, but through CFC manufactured from large plasma pools which did not undergo VI at the time. In countries like Belgium where hemophilia treatment was almost entirely based on cryo, the HIV infection rate remained rather low as compared to countries where replacement therapy was extensively and systematically performed with CFC (e.g., in Germany, USA, etc.).

"Cryo is evil" was the label which was given by many at the time to "native" cryo when most of today's safety interventions were not in place at the time (e.g., NAT testing, stringent donor selection, quality systems, haemovigilance, etc.). Since then, the negative branding has often been generalised incorrectly to all forms of cryo (quarantined, VI-treated, etc.).

For CFC, the perception has changed with time through continued information delivered with the products. When manufacturing of these products included systematically one or more VI steps, they became viral-safe and the perception of the users changed to a positive.

On the other hand, cryo continued to be used in its "native" form because no specific technology was available until 2010 to virus inactivate cryo. When PR technologies became available to make Cryo-VI, they were not very much used at a global level.

"Native" untreated cryo continued to be used at large and it has kept its "bad" reputation (although it saves lives every day). Even nowadays, most stakeholders do not make an objective difference between "native" and "virus inactivated" cryo: for many of them, all cryos continue to be "dangerous" or "posing a threat", whether they are "native" or made safe by VI.

CFC have stripped off their negative image, while Cryo-VI has not yet been successful in correcting its reputation.

As can be seen from the above, Cryo-VI encounters many different kinds of opposition, hindrance, resistance and distrust: therefore, Cryo-SD/F has not yet reached those patient populations for which it could really make a vital difference in terms of safety and availability and where "hemophiliacs" continue to be deprived of any form of effective treatment.

How to overcome these barriers?

Taking into account all hindering factors, what can or should be done to alleviate the existing unbearable situation for patients with bleeding disorders in the developing world?

Recently, a global initiative has been launched to mobilize forces around the globe to promote and to facilitate implementation of local preparation of Cryo-VI in developing countries.

This worldwide movement is a collaborative effort of different international partnering organisations (like WHO, ISBT and possibly others) and national stakeholders in resource limited countries (competent authorities, blood suppliers, patient organisations, etc.).

The Global Initiative on local preparation of Cryo-VI in developing countries ("Local Cryo-VI in l-HDI") is presented in a separate article in this special issue of *AOB* (18).

Conclusions

Treatment of patients with bleeding disorders (especially with hemophilia A) has significantly improved in general, but not all problems have been solved. For many years, no major progress has been made in increasing availability of therapeutic products in developing countries and in lowering the risk of inhibitor formation in the world.

Part of the solution to solve existing problems is VI of cryo (like Cryo-VI using VIPS medical device for Cryo-SD/F®) by:

- Rendering cryo safe;

- ❖ Allowing for reliable and independent supply through local production;
- ❖ Reducing the incidence of inhibitor formation;
- ❖ Managing the costs for hemophilia treatment in a responsible way.

Cryo-SD/F can have substantial benefits for patients with bleeding disorders in developing countries, ensuring availability, accessibility, affordability, sustainability and independence, involving communities through blood donation, increasing productivity of existing infrastructures, equipment, staff, etc.

And, last but not least, Cryo-SD/F can have another major impact by lowering inhibitor formation, in developing countries as well as in developed ones.

In the past, VI-technology has not been rolled out at large and its enormous potential for bringing change is not fully exploited. The reasons for this are multiple, but insufficient information and education on Cryo-VI, incomplete clinical guidelines as well as poor advocacy with the stakeholders for Cryo-VI in the treatment of bleeding disorders are some decisive factors for the limited use of Cryo-SD/F.

Recently, a global initiative has been launched to promote local preparation of Cryo-VI (Cryo-SD/F) in developing countries and to solve existing supply issues. At the same time, the worldwide movement will also further increase alertness for inhibitor formation and facilitate serious consideration of Cryo-VI for the treatment of hemophilia A to cope with this persistent and underestimated problem.

Cryo-VI offers a unique opportunity to concomitantly manage the most prominent problems in hemophilia care: product shortage in resource limited countries and inhibitor formation worldwide. Beyond reasonable doubt, Cryo-VI can significantly contribute to solve existing problems with the treatment of patients with bleeding disorders in the world: its potential and its relevance have been neglected for too long.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aob.2018.01.04). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the manuscript and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. World Federation of Hemophilia (WFH) Annual Report 2016. Available online: http://www.wfh.org
2. Peyvandi F, Mannucci PM, Garagiola I, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. N Engl J Med 2016;374:2054-64.
3. Calvez T, Chambost H, d'Oiron R, et al. Analyses of the FranceCoag cohort support differences in immunogenicity among one plasma-derived and two recombinant factor VIII brands in boys with severe hemophilia A. Haematologica 2018;103:179-89.
4. EDQM. Guide to the preparation, use and quality assurance of blood components. Rec. (95) 15. 18th edition. Strasbourg: Council of Europe Press 2015.
5. AuBuchon JP. Current status of pathogen inactivation methods. ISBT Sci Ser 2010;5:125-33.
6. Burnouf T, Goubran HA, Radosevich M, et al. A minipool process for solvent-detergent treatment of cryoprecipitate at blood centres using a disposable bag system. Vox Sang 2006;91:56-62.
7. Lin L, Dikeman R, Molini B, et al. Photochemical treatment of platelet concentrates with amotosalen and long-wavelength ultraviolet light inactivates a broad spectrum of pathogenic bacteria. Transfusion 2004;44:1496-504.
8. Goodrich RP, Edrich RA, Li J, et al. The Mirasol PRT system for pathogen reduction of platelets and plasma: an overview of current status and future trends. Transfus Apher Sci 2006;35:5-17.

9. Burnouf T, Goubran HA, Radosevich M, et al. A process for solvent/detergent treatment of plasma for transfusion at blood centers that use a disposable-bag system. Transfusion 2006;46:2100-8.
10. Horowitz B, Prince AM, Horowitz MS, et al. Viral safety of solvent-detergent treated blood products. Dev Biol Stand 1993;81:147-61.
11. El-Ekiaby M, Goubran HA, Radosevich M, et al. Pharmacokinetic study of minipooled solvent/detergent-filtered cryoprecipitate factor VIII. Haemophilia 2011;17:e884-8.
12. El-Ekiaby M. Pathogen Reduced Cryoprecipitate as an affordable option for patients with inherited bleeding disorders in developing countries, Egypt Experience. Annals of Blood 2017. [In press].
13. World Health Organisation (WHO). List of Essential Medicines. Available online: http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf
14. International Society of Blood Transfusion (ISBT). Revised Code of Ethics of ISBT 2017. Available online: https://uniregistry.com/market/domain/isbt.org?landerid=www5a67e0d3a8a646.16454176
15. Marketing Research Bureau (MRB). International Directory of Plasma Fractionators 2010. Orange: Marketing Research Bureau 2010.
16. Peerlinck K, Rosendaal FR, Vermylen J. Incidence of inhibitor development in a group of young hemophilia A patients treated exclusively with lyophilized cryoprecipitate. Blood 1993;81:3332-5.
17. World Federation of Hemophilia (WFH). Guidelines for the Management of Hemophilia 2012. 2nd edition. Available online: https://www.wfh.org/en/page.aspx?pid=492
18. Faber JC. A global initiative on local preparation of virus inactivated cryoprecipitate in developing countries. Ann Blood 2017;2:21.

doi: 10.21037/aob.2018.01.04
Cite this article as: Faber JC. Role of virus inactivated cryoprecipitate in the treatment of bleeding disorders. Ann Blood 2018;3:21.

