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SHORT REPORT

Independent evaluation of tolerance of therapeutic plasma inactivated by amotosalen-HCl–UVA (Intercept™) over a 5-year period of extensive delivery

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Amotosalen-HCl–UVA (AI) is a process to inactivate pathogens in therapeutic plasma (FFP). Tolerance is the main residual issue in FFP transfusion, and only large series observations are powered enough to identify significantly elevated levels of hazards. We report here on 15 133 new transfusions of AI-FFP, over the previously published 36 035, which in all represents one of the largest series observed by means of a highly standardized surveillance (51 168 observations). There is no noticeable difference in terms of tolerance of AI-FFP compared to 5875 transfusions of Quarantine (Q)-FFP. There was no significant difference in terms of advance events, between the two types of FFP ($P = 0{\cdot}98$); further, no difference was recorded either when the total number of AI-FFP (51 168) was compared to the corresponding number of Q-FFP (5875; $P = 0{\cdot}62$).

Key words: amotosalen, haemovigilance, pathogen reduction, safety, therapeutic plasma.

As of 2014, the French Blood Establishment (EFS) prepares and distributes Fresh Frozen Plasma (FFP) issued from male donors collected only by apheresis donation (qualified as HLA antibody negative). FFP is leucodepleted ($<10^{-4}$ residual leucocytes/l). Three types of plasma were delivered during the observation period of this study [2009–2013: solvent–detergent (SD), 60 day quarantine (Q) and amotosalen inactivated (AI)]. The AI system (Intercept™; Concord, CA, USA) has been authorized for plasma in France in 2006 and implemented by the fall of 2009.

The Auvergne-Loire regional blood centre of EFS has issued 51 168 units of about 200 ml of AI-FFP during the observation period, which represents one of the largest series to be reported so far.

Regarding AI-FFP, haemostatic efficacy has been reported elsewhere and is considered satisfactory [1, 2]. Besides, tolerance to therapeutic plasma is a general concern [3], especially when large amounts of plasma are delivered to patients, for example plasma exchanges; tolerance has been re-emphasized since reports of allergic reactions associated with methylene blue (MB)-inactivated FFP have been reported in France [4] (though apparently not in other countries) [5], leading to its discontinuation.

Our previous survey of plasma delivery over a 10-year observation period that compared four FFP types (Q, SD, MB and AI) did not detect noteworthy differences in terms of tolerance between them [6]. However, as severe intolerance is a rare event, the study requires power with a larger number of observations. To achieve this goal, we pursued the collection of events reported by a strengthened haemovigilance. To minimize variability within interpretation of Adverse Events (AE), especially of low severity and low accountability, we considered one regionally harmonized system only [6].

Here, we compared data obtained with AI-FFP with Q-FFP, as Q is not manipulated (the non-manipulation provides a suitable comparator); there were basically two options: (1) the comparison with Q-FFP units over a similar period of time, offering the advantage of a strictly

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Table 1 Actual number of Q- and AI-FFP units issued yearly and considered for evaluating plasma tolerance. Arrows indicate the period under review

	No. of FFP issued units per year under review													
	2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**Total**
Q-FFP	6604	9346	9566	8966	7524	5645	5699	4723	Q-FFP was no longer delivered in France since it has been reintroduced by the end of year 2012			2796	3079	
									Discontinued			Merged: 5875		5875
AI-FFP	N/A					The AI procedure (PRT) for plasma has been authorized by Afssaps/ ANSM in 2006; in process by the end of year 2009 in the Auvergne-Loire EFS			2201	13 348	13 532	10 572	11 515	
														51 168

FFP, fresh frozen plasma.

parallel level of declaration, but the number of FFP components issued during the survey period was not equal (from far: ×10); (2) the comparison of equal numbers of issued AI- and Q-FFP, offering the advantage of the math, but the disadvantage of the irregularity of FFP delivery of either type over time (with little overlap). Actual numbers of FFP issued units per year are quoted in Table 1.

Reported here are AEs of severity classified as grade 2 and above, with an imputation of 1 and above. The methods for collecting information and the declaration system are the same as previously reported [6]. The statistical evaluation was performed by means of a chi-squared test with a Yates correction, to protect against bias linked to discrepancies in numbers (Table 2); tests were further cross-checked by means of the exact Fisher's test.

Data are shown in Table 2: Table 2A presents a comparison of AEs over the last 2-year period for each FFP type (15 133 new AI-FFP transfusions and 5875 Q-FFP transfusions); and Table 2B sums up comparisons of respective FFP reactions in series of 51 168 individual observations concerning AI-FFP and 5875 total observations for Q-FFP (the number of Q-FFP transfusions is equal in two arms as this type of plasma has been discontinued before being reintroduced later in France, at a time that corresponds exactly to the second part of this survey). Comparisons of AEs aligned to ~51 000 in each group have been disregarded because of possible evolution in declaration overtime (>10 years in the Q-group and a little more than 4 years only for AI-FFP). Statistical tests with corrected chi-square showed no difference in each set of data (new observations and total observations). Almost exactly similar '*P*' values in both series were obtained when a Fisher's test was applied as a cross-reference.

In all, when two FFP types (Q- and AI-) – that benefited from the same safety additional steps, in particular towards the anti-HLA Abs applied in 2012 – were compared concurrently with regard to AEs (including minor AEs), using exactly the same level of reports, there was no difference. The statistical tests used were chosen to eliminate the bias that might have happened because of the

Table 2 Comparison of FFP tolerance with two types of plasma in one regional setting of the national blood service in France (period 2001–2013; 51 168 amotosalen-HCl–UVA inactivated (AI) FFP units); the accountability used for recording the hazardous events was 1 and above

	Severity 2	**Severity 3**	**Severity 4**	**Total**	**No. observations**	**Incidence**	**Statistical significance**
(A) New FFP transfusions							
AI-FFP	3	2	0	5	15 133	0·00033	NS
Q-FFP	2	0	0	2	5875	0·00034	$P = 0·98$
(B) Comparison between observations with 2 FFP types (same period of time)							
AI-FFP	5	7	0	12	51 168	0·00024	NS
Q-FFP	2	0	0	2	5875	0·00034	$P = 0·62$

FFP, fresh frozen plasma.

Table 3 Clinical details on adverse events recorded after the transfusion of AI-FFP and Q-FFP

Type of plasma	Date	Severity	Diagnostics	Associated pathology
AI-FFP	December 2011	3	Allergy (shock)	
AI-FFP	April 2012	2	Allergy (localized urticaria)	Associated urticaria on puncture sites; latex allergy suspected
Q-FFP	November 2012	2	Allergy (cutaneous rash and dyspnea)	
Q-FFP	December 2012	2	Allergy (localized urticaria)	
AI-FFP	January 2013	3	Oedema (face and thorax); considered allergic type	Associated urticarial on puncture sites; latex allergy suspected
AI-FFP	March 2013	2	Hypotension; considered allergic type	Associated allergy to antibiotics and disinfectant
AI-FFP	September 2013	2	Hypotension; considered allergic type	Suspected sepsis (*Staphylococcus hominis*)

discrepancies in numbers (about three times more AI- than Q-PPF); however, there still is a possibility that the study was not powered enough to warrant firm conclusions. It is nevertheless difficult to draw firm conclusions on this analysis because the limitation of anti-HLA antibodies concerned twice more new AI- than Q-FFP units [7].

An ancillary objective of the present survey was to report on AEs that were allergic in nature, or reported as allergic type, as allergic reaction is the main diagnosis of intolerance to therapeutic plasma; although not exclusively [8], it seems to be largely dependent on individual clinical factors in the recipient [9, 10]. The AI-process has been particularly scrutinized by physicians in charge of surveillance and vigilance in transfusion wards, to make sure that AI does not associate to excess reports of allergy, as MB possibly did (Table 3 gives details on the major AEs recorded in this survey; of note, no TRALI was recorded before and after the anti-HLA antibody screening, for either type of plasma. Each recorded AE proved to be allergic in nature, either with neat symptomatology or with hypotension, now acknowledged to be an allergic-type reaction. Of further note, five of the six allergic-type reactions attributed to therapeutic plasma happened in patients displaying simultaneously symptoms of allergy to another topic). In all, as can be said after more than 51 000 close observations, AI-PPF tolerance proves to be good.

Conflict of interests

Certain authors have received travel awards or invitation to meetings by the following industrial companies: Cerus; MacoPharma; and TerumoBCT. No conflict of interest is relevant to this study.

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