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Early View

Research letter

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Alpha-1 antitrypsin deficiency (AATD) is a hereditary disorder characterised by an abnormally low concentration of functional alpha-1 antitrypsin (AAT) in blood and tissues [1]. The primary role of AAT is to protect elastin-containing tissues, most notably the lung, against the destructive activity of proteolytic enzymes [2]. Patients with severe AATD present with serum AAT concentrations below 11 µM and are prone to destruction of the lung tissue, often developing respiratory symptoms and emphysema in the fourth or fifth decade of life [3, 4].

For three decades, treatment with intravenous AAT has been available, yet only recently was the RAPID-RCT, a 2-year placebo-controlled trial in 180 AATD patients, able to demonstrate that weekly therapy with 60 mg/kg body weight AAT reduces the loss of lung tissue [5] and slows disease progression [6]. The RAPID OLE study followed 130 of these patients for a further 2 years [6].

The licensed dose recommended by current guidelines is the weekly infusion of 60 mg AAT per kg body weight [7-9]. This regimen can be time consuming, costly and inconvenient and alternative dosing regimens have been proposed [10]. However, there is a paucity of clinical trial data supporting the efficacy, safety and tolerability of alternative dosing regimens [11].

In a post-hoc analysis we investigated the safety and tolerability of 60 mg/kg and placebo infusions to 120 mg/kg infusions administered in the RAPID-RCT; bi-weekly infusions of either placebo or 120 mg/kg were administered to cover planned drug holidays. A pooled comparison of all bi-weekly 120 mg/kg infusions during the 4-year RAPID program was also performed.

Treatment emergent adverse events (TEAEs) were analysed and the severity graded as mild (did not interfere with routine activities), moderate (interfered with routine activities), severe (impossible to perform routine activities). Serious adverse events (SAEs) were defined as life-threatening TEAEs resulting in hospitalisation, prolonged hospitalisation, significant disability or death.

Two different measures to compare the adverse event rates were calculated. The exposure adjusted event rates (EAERs) divided all TEAEs during the study conduct by the cumulative exposure of the respective group (60 or 120 mg/kg AAT or matching placebo). The infusion adjusted event rates (IAERs) compared the TEAE rates occurring in the 7-day period prior to and following a bi-weekly 120 mg/kg infusion or matching placebo, i.e. an infusion sequence.

Differences in EAERs were assessed by a normal approximation test. The McNemar test was used for the intra-individual comparison of the occurrence of TEAEs in the 7 days before the first double dose (i.e. after 60 mg/kg) and in the 7 days after the last 120 mg/kg AAT dose. Reported p-values are two-sided without adjustment for multiple testing.

A total of 75 of 93 patients (80.6% of the AAT group) had at least one bi-weekly infusion of AAT during RAPID-RCT, compared to 70 of 87 patients (80.5%) that received bi-weekly placebo infusions. Baseline characteristics are given in Fig. 1.

Bi-weekly infusions comprised 4.3% of all AAT and 5.2% of all placebo administrations across both studies, respectively. The calculated drug exposure for 60 mg/kg infusions weekly was more than ten times higher than for the bi-weekly 120 mg/kg infusions (AAT: 158.20 versus 14.09 subject years [SY], placebo: 134.92 versus

15.55 SY). When all AAT bi-weekly doses were pooled across RAPID-RCT and OLE, 933 infusions over 884 infusion sequences in 137 patients were identified (mean 6.45 ± 4.26, range 1-21) (Fig. 1).

The EAERs were 7.32 versus 6.80 for weekly 60 mg/kg AAT and placebo (p=0.103) and 7.10 versus 7.50 for bi-weekly 120 mg/kg AAT and placebo infusions (p=0.754), respectively (Fig. 1). The proportion of patients who experienced a TEAE during the infusion sequences was 33.3% in the bi-weekly 120 mg/kg group compared to 35.7% in bi-weekly placebo and 37.3% in weekly 60 mg/kg or 37.1% in weekly placebo. The corresponding IAER were 0.1622 versus 0.1386 for 120 mg/kg AAT and placebo infusions (p=0.754) and 0.1464 versus 0.1265 for 60 mg/kg AAT versus weekly placebo (p=0.103). Within 24 hours of infusion when volume-related TEAEs would be expected, IAERs were 0.0374 for 120 mg/kg AAT versus 0.0301 for bi-weekly placebo, and 0.0343 for 60 mg/kg AAT versus 0.0361 for weekly placebo. IAERs in the delayed start OLE subgroup were 0.0645 in the 60 mg compared to 0.1111 in the 120 mg periods (p=0.0386). During all double dose infusion sequences four treatment related TEAEs were reported in association with the bi-weekly 120 mg/kg infusions (joint pain and headache in one patient, exacerbation and headache in two patients; cumulative IAER=0.0125), compared to a single treatment related report of rash in the placebo bi-weekly regimen (IAER=0.0030).

During RAPID-RCT and OLE 16% of patients reported a TEAE within 24 hours of infusion, and 25% reported TEAEs within 72 hours in either treatment group. A higher proportion of patients experienced a TEAE within 7 days following a bi-weekly 120 mg/kg infusion (43.8%) than 7 days prior to double dosing (34.3%). The number of TEAEs per infusion was 0.1267 for 120 mg/kg and 0.1041 for 60 mg/kg, respectively. Most TEAEs were mild or moderate in intensity: 94.6% with 60 mg/kg and, 92.9% with bi-weekly 120 mg/kg. An analysis of TEAEs by System Organ Class showed similar distributions in all subgroups (data not shown).

In RAPID-RCT four SAEs were reported during the infusion sequences three SAEs with bi-weekly 120 mg/kg (malignant tumour in the bladder, transurethral resection of the prostate, and small bowel obstruction), one SAE was reported with 60 mg/kg (chest pain), and none were reported with placebo. In RAPID-OLE 8 SAEs occurred (4 patients with exacerbations, one patient with 3 AEs: pneumonia, abscess and chronic carnification of the lobe, one patient with a brain thrombus). One of the 12 SAEs was considered to be drug related (chronic carnification).

To our knowledge this is the first systematic analysis of the adverse event rates and profile for two different AAT dosing patterns compared to matching placebo. Rates of TEAEs were comparable between all subgroups. In particular, there was no difference in event rates within 72 hours after infusion or causally related events, demonstrating that doubling the dose and infusion volume is not associated with adverse volume effects in the investigated population. The significant difference in the OLE delayed start group in favour of the 60 mg group was driven by an low rate of reported TEAEs compared to 60 mg RCT and early start subgroups in an analysis that was not adjusted for multiple testing.

Bi-weekly dosing with 120 mg/kg AAT is a convenient alternative to the recommended weekly dosing pattern that considerably reduces the organisational and medicinal burdens of weekly infusions, e.g., travelling to an infusion site, lifestyle disruptions, and all procedures associated with infusions including scheduling, set up and administration. This study is the largest body of evidence supporting the safety and tolerability of the bi-weekly 120 mg/kg pattern. There were no indications of changes in the type, frequency, duration or severity of

TEAEs reported. This is in line with the previously published reports of the safety of augmentation therapy at doses > 60 mg/kg obtained in smaller cohorts [12, 13].

Data from population pharmacokinetic simulations predicted that trough levels above the 11 µM protective threshold will be maintained in the majority of patients treated with bi-weekly 120 mg/kg infusions [14], an important prerequisite when considering alternative administration regimens. However bi-weekly 120 mg/kg infusions were administered infrequently and sporadically throughout the RAPID program due to planned drug holidays and no conclusions can be drawn regarding the impact of the bi-weekly regimen on rates of lung density decline. The evaluation of long term weekly 120 mg/kg infusions for efficacy, safety and tolerability outcomes is currently being evaluated in clinical trials [15].

In conclusion, bi-weekly infusions of 120 mg/kg AAT has a similar safety and tolerability profile to 60 mg/kg and both are comparable to placebo in patients with severe AATD. Bi-weekly dosing is expected to enhance the convenience of treatment with AAT.
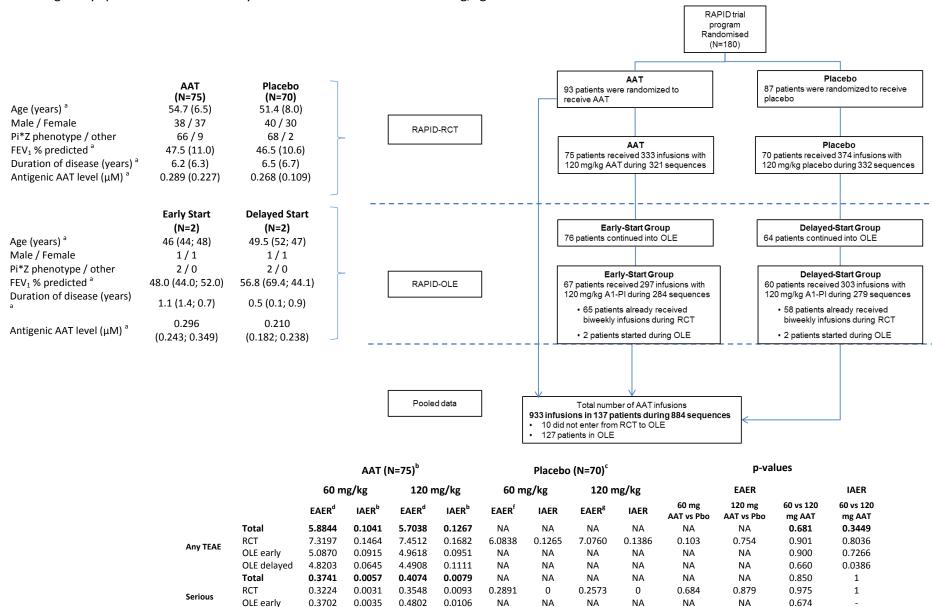
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Figure 1: Patient flow, demographics and disease characteristics at baseline for patients who received at least one biweekly 120 mg/kg AAT infusion or matching placebo during RAPID-RCT or RAPID-OLE, and safety of AAT infusion sequences compared to placebo in RAPID-RCT occurring 7 days prior to and within 7 days after the administration of 120 mg/kg

	AAT (N=75)	Placebo (N=70)
Age (years) [a]	54.7 (6.5)	51.4 (8.0)
Male / Female	38 / 37	40 / 30
Pi*Z phenotype / other	66 / 9	68 / 2
FEV_1 % predicted [a]	47.5 (11.0)	46.5 (10.6)
Duration of disease (years) [a]	6.2 (6.3)	6.5 (6.7)
Antigenic AAT level (μM) [a]	0.289 (0.227)	0.268 (0.109)

	Early Start (N=2)	Delayed Start (N=2)
Age (years) [a]	46 (44; 48)	49.5 (52; 47)
Male / Female	1 / 1	1 / 1
Pi*Z phenotype / other	2 / 0	2 / 0
FEV_1 % predicted [a]	48.0 (44.0; 52.0)	56.8 (69.4; 44.1)
Duration of disease (years) [a]	1.1 (1.4; 0.7)	0.5 (0.1; 0.9)
Antigenic AAT level (μM) [a]	0.296 (0.243; 0.349)	0.210 (0.182; 0.238)

RAPID trial program Randomised (N=180)

AAT — 93 patients were randomized to receive AAT

Placebo — 87 patients were randomized to receive placebo

RAPID-RCT

AAT — 75 patients received 333 infusions with 120 mg/kg AAT during 321 sequences

Placebo — 70 patients received 374 infusions with 120 mg/kg placebo during 332 sequences

Early-Start Group — 76 patients continued into OLE

Delayed-Start Group — 64 patients continued into OLE

RAPID-OLE

Early-Start Group — 67 patients received 297 infusions with 120 mg/kg A1-PI during 284 sequences
- 65 patients already received biweekly infusions during RCT
- 2 patients started during OLE

Delayed-Start Group — 60 patients received 303 infusions with 120 mg/kg A1-PI during 279 sequences
- 58 patients already received biweekly infusions during RCT
- 2 patients started during OLE

Pooled data

Total number of AAT infusions — **933 infusions in 137 patients during 884 sequences**
- 10 did not enter from RCT to OLE
- 127 patients in OLE

		AAT (N=75) [b]				Placebo (N=70) [c]				p-values			
		60 mg/kg		120 mg/kg		60 mg/kg		120 mg/kg		EAER		IAER	
		EAER[d]	IAER[b]	EAER[d]	IAER[b]	EAER[f]	IAER	EAER[g]	IAER	60 mg AAT vs Pbo	120 mg AAT vs Pbo	60 vs 120 mg AAT	60 vs 120 mg AAT
Any TEAE	Total	5.8844	0.1041	5.7038	0.1267	NA	NA	NA	NA	NA	NA	0.681	0.3449
	RCT	7.3197	0.1464	7.4512	0.1682	6.0838	0.1265	7.0760	0.1386	0.103	0.754	0.901	0.8036
	OLE early	5.0870	0.0915	4.9618	0.0951	NA	NA	NA	NA	NA	NA	0.900	0.7266
	OLE delayed	4.8203	0.0645	4.4908	0.1111	NA	NA	NA	NA	NA	NA	0.660	0.0386
Serious	Total	0.3741	0.0057	0.4074	0.0079	NA	NA	NA	NA	NA	NA	0.850	1
	RCT	0.3224	0.0031	0.3548	0.0093	0.2891	0	0.2573	0	0.684	0.879	0.975	1
	OLE early	0.3702	0.0035	0.4802	0.0106	NA	NA	NA	NA	NA	NA	0.674	-
	OLE delayed	0.4503	0.0108	0.3939	0.0036	NA	NA	NA	NA	NA	NA	0.950	-

Data are mean (standard deviation) or number of patients. Where only two data points were available, the individual data are shown in brackets.

EAER, exposure adjusted event rates (number of events/subject years). Parameter that takes into account all TEAEs during the trial except the periods with unknown infusion volumes which were omitted (64 of 29,076 infusions).

IAER, infusion-adjusted event rate (number of events/number of infusion sequences). Intra-individual comparison of TEAEs that includes individuals that have received 120 mg/kg biweekly infusions.

An infusion sequence consisted of a 60 mg/kg weekly infusion or matching placebo followed by one or more infusions of biweekly 120 mg/kg or matching placebo. In this analysis the number of TEAEs occurring within the 7-day period prior to a double dose infusion whilst exposed to 60 mg/kg or matching placebo was compared those occurring in the 7-day period following the biweekly 120 mg/kg infusion or matching placebo.

[a]   Data obtained at baseline of RCT.

[b]   Number of biweekly infusions sequences with AAT during RCT=321 and during OLE=653, total=884.

[c]   Number of biweekly infusion sequences with placebo during RCT=332.

[d]   Drug exposure for AAT group 60 mg weekly in RAPID-RCT was subject years (SY)=158.20; number of infusions (I)=8098; RAPID-OLE early treatment group SY=135.02, I=6948; RAPID-OLE late treatment group SY=113.27, I=5814.

[e]   Drug exposure for AAT group 120 mg weekly in RAPID-RCT was SY=14.09; I=333; RAPID-OLE early treatment group SY=12.50, I=297; RAPID-OLE late treatment group SY=12.69, I=303.

[f]   Drug exposure for placebo group 60 mg weekly in RAPID-RCT was SY=134.92, I=6845.

[g]   Drug exposure for placebo group 60 mg weekly in RAPID-RCT was SY=15.55, I=374.

-: not applicable; AAT: alpha1 antitrypsin; FEV_1: forced expiratory volume in 1 s; N: number of patients; OLE: open label extension; RAPID: Randomised trial of augmentation therapy in Alpha-1 Proteinase Inhibitor Deficiency; RCT: randomised controlled trial; TEAE: treatment emergent adverse event.