Safety of biweekly α_1-antitrypsin treatment in the RAPID programme

To the Editor:

α_1-antitrypsin (α_1-AT) deficiency is a hereditary disorder characterised by an abnormally low concentration of functional α_1-AT in blood and tissues [1]. The primary role of α_1-AT is to protect elastin-containing tissues, most notably the lung, against the destructive activity of proteolytic enzymes [2]. Patients with severe α_1-AT deficiency present with serum α_1-AT concentrations <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 α_1-AT has been available, yet only recently was the RAPID (Randomised Trial of Augmentation Therapy in Alpha-1 Proteinase Inhibitor Deficiency)-Randomised Controlled Trial (RCT), a 2-year placebo-controlled trial in 180 α_1-AT deficiency patients, able to demonstrate that weekly therapy with 60 mg·kg^{-1} body weight α_1-AT reduces the loss of lung tissue [5] and slows disease progression [6]. The RAPID-Open Label Extension (OLE) study followed 130 of these patients for a further 2 years [6].

The licenced dose recommended by current guidelines is the weekly infusion of 60 mg·kg^{-1} body weight α_1-AT [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^{-1} and placebo infusions to 120 mg·kg^{-1} infusions administered in the RAPID-RCT; biweekly infusions of either placebo or 120 mg·kg^{-1} were administered to cover planned drug holidays. In addition, a pooled comparison of all biweekly 120 mg·kg^{-1} infusions during the 4-year RAPID programme was 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) or 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^{-1} α_1-AT or matching placebo). The infusion-adjusted event rates (IAERs) compared the TEAE rates occurring in the 7-day period prior to and following a biweekly 120 mg·kg^{-1} infusion or matching placebo, *i.e.* an infusion sequence.

Differences in EAERs were assessed using 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^{-1}) and in the 7 days after the last 120 mg·kg^{-1} α_1-AT dose. Reported p-values are two-sided without adjustment for multiple testing.

75 (80.6% of the α_1-AT group) of 93 patients had at least one biweekly infusion of α_1-AT during RAPID-RCT, compared to 70 (80.5%) of 87 patients who received biweekly placebo infusions. Baseline characteristics are given in figure 1.

Biweekly infusions comprised 4.3% of all α_1-AT and 5.2% of all placebo administrations across both studies. The calculated drug exposure for 60 mg·kg^{-1} infusions weekly was >10 times higher than for the biweekly 120 mg·kg^{-1} infusions (α_1-AT 158.20 *versus* 14.09 subject-years, placebo 134.92 *versus*

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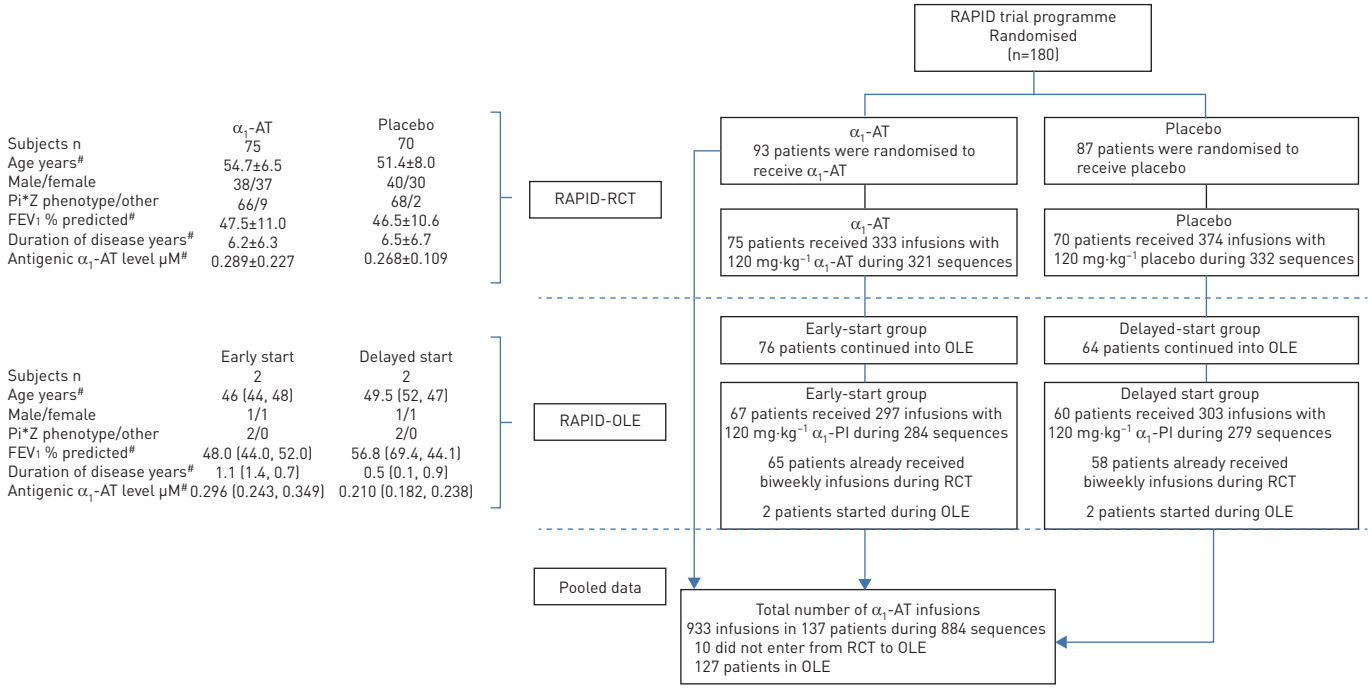

		α1-AT (n=75)¶				Placebo (n=70)+				p-values			
		60 mg·kg−1		120 mg·kg−1		60 mg·kg−1		120 mg·kg−1		EAER			IAER
		EAER§	IAER¶	EAERf	IAER¶	EAER##	IAER¶	EAER¶¶	IAER	60 mg α1-AT *versus* placebo	120 mg α1-AT *versus* placebo	60 *versus* 120 mg α1-AT	60 *versus* 120 mg α1-AT
Any TEAE	Total	5.8844	0.1041	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	

FIGURE 1 Patient flow, demographics and disease characteristics at baseline for patients who received at least one biweekly 120 mg·kg^{-1} α_1-antitrypsin (α1-AT) infusion or matching placebo during RAPID (Randomised Trial of Augmentation Therapy in Alpha-1 Proteinase Inhibitor Deficiency)-Randomised Controlled Trial (RCT) or RAPID-Open Label Extension (OLE), and safety of α_1-AT infusion sequences compared to placebo in RAPID-RCT occurring 7 days prior to and within 7 days after the administration of 120 mg·kg^{-1}. Data are presented as mean±SD or n. Where only two data points were available, the individual data are shown in brackets. EAER: exposure-adjusted event rates (events per subject-years), parameter that takes into account all treatment-emergent adverse events (TEAEs) during the trial except the periods with unknown infusion volumes, which were omitted (64 out of 29 076 infusions); IAER: infusion-adjusted event rate (events per n infusion sequences), intra-individual comparison of TEAEs that includes individuals that have received 120 mg·kg^{-1} biweekly infusions. An infusion sequence consisted of a 60 mg·kg^{-1} weekly infusion or matching placebo followed by one or more infusions of biweekly 120 mg·kg^{-1} or matching placebo. In this analysis the number of TEAEs occurring within the 7-day period prior to a double-dose infusion while exposed to 60 mg·kg^{-1} or matching placebo was compared with those occurring in the 7-day period following the biweekly 120 mg·kg^{-1} infusion or matching placebo; Pi*Z: α_1-AT deficiency; FEV_1: forced expiratory volume in 1 s; PI: proteinase inhibitor; NA: not applicable. #: data obtained at baseline of RCT. ¶: biweekly infusion sequences with α_1-AT during RCT n=321 and during OLE n=563, total n=884. +: biweekly infusion sequences with placebo during RCT n=332. §: drug exposure for α_1-AT group 60 mg weekly in RAPID-RCT was 158.20 subject-years; number of infusions (I) 8098; RAPID-OLE early treatment group 135.02 subject-years, I=6948; RAPID-OLE late treatment group 113.27 subject-years, I=5814. f: drug exposure for α_1-AT group 120 mg weekly in RAPID-RCT was 14.09 subject-years, I=333; RAPID-OLE early treatment group 12.50 subject-years, I=297; RAPID-OLE late treatment group 12.69 subject-years, I=303. ##: drug exposure for placebo group 120 mg weekly in RAPID-RCT was 134.92 subject-years, I=6845. ¶¶: drug exposure for placebo group 120 mg weekly in RAPID-RCT was 15.55 subject-years, I=374.

15.55 subject-years). When all α_1-AT biweekly doses were pooled across RAPID-RCT and -OLE, 933 infusions over 884 infusion sequences in 137 patients were identified (mean±SD 6.45±4.26, range 1–21) (figure 1).

The EAERs were 7.32 *versus* 6.08 for weekly 60 mg·kg^{-1} α_1-AT and placebo (p=0.103) and 7.45 *versus* 7.08 for biweekly 120 mg·kg^{-1} α_1-AT and placebo infusions (p=0.754), respectively (figure 1). The proportion of patients who experienced a TEAE during the infusion sequences was 33.3% in the biweekly 120 mg·kg^{-1} group compared to 35.7% in biweekly placebo and 37.3% in weekly 60 mg·kg^{-1} or 37.1% in weekly placebo. The corresponding IAER were 0.1682 *versus* 0.1386 for 120 mg·kg^{-1} α_1-AT and placebo

infusions (p=0.754) and 0.1464 *versus* 0.1265 for 60 mg·kg^{-1} α_1-AT *versus* weekly placebo (p=0.103). Within 24 h of infusion, when volume-related TEAEs would be expected, IAERs were 0.0374 for 120 mg·kg^{-1} α_1-AT *versus* 0.0301 for biweekly placebo, and 0.0343 for 60 mg·kg^{-1} α_1-AT *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 TEAEs were reported in association with the biweekly 120 mg·kg^{-1} infusions (one patient reported joint pain and headache, one had an exacerbation and one complained of headache; cumulative IAER=0.0125), compared to a single treatment-related report of rash in the placebo biweekly regimen (IAER=0.0030).

During RAPID-RCT and -OLE 16% of patients reported a TEAE within 24 h of infusion and 25% reported TEAEs within 72 h in either treatment group. A higher proportion of patients experienced a TEAE within 7 days following a biweekly 120 mg·kg^{-1} 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^{-1} and 0.1041 for 60 mg·kg^{-1}. Most TEAEs were mild or moderate in intensity: 94.6% with 60 mg·kg^{-1} and 92.9% with biweekly 120 mg·kg^{-1}. 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 biweekly 120 mg·kg^{-1} (malignant tumour in the bladder, transurethral resection of the prostate and small bowel obstruction); one SAE was reported with 60 mg·kg^{-1} (chest pain); and none were reported with placebo. In RAPID-OLE eight SAEs occurred (exacerbations n=4; three adverse events (pneumonia, abscess and chronic carnification of the lobe) in a single patient and brain thrombus n=1). 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 α_1-AT 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 h 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 a low rate of reported TEAEs compared to 60 mg RCT and early-start subgroups in an analysis that was not adjusted for multiple testing.

Biweekly dosing with 120 mg·kg^{-1} α_1-AT is a convenient alternative to the recommended weekly dosing pattern, and which 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 biweekly 120 mg·kg^{-1} pattern. There were no indications of changes in the type, frequency, duration or severity of TEAEs reported. This is in line with previously published reports of the safety of augmentation therapy at doses >60 mg·kg^{-1} 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 biweekly 120 mg·kg^{-1} infusions [14], an important prerequisite when considering alternative administration regimens. However, biweekly 120 mg·kg^{-1} infusions were administered infrequently and sporadically throughout the RAPID programme due to planned drug holidays, and no conclusions can be drawn regarding the impact of the biweekly regimen on rates of lung density decline. The evaluation of long-term weekly 120 mg·kg^{-1} infusions for efficacy, safety and tolerability outcomes is currently being evaluated in clinical trials [15].

In conclusion, biweekly infusions of 120 mg·kg^{-1} α_1-AT has a similar safety and tolerability profile to 60 mg·kg^{-1} and both are comparable to placebo in patients with severe α_1-AT deficiency. Biweekly dosing is expected to enhance the convenience of treatment with α_1-AT.

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This study is registered at ClinicalTrials.gov with identifier numbers NCT00261833 and NCT00670007. CSL Behring has previously published both the RAPID and RAPID OLE protocols with the *Lancet* and would be happy to provide these upon request in conjunction with this publication. This is a straightforward, *post hoc* safety analysis from these trials. At this time, CSL Behring does not plan to release the de-identified individual patient data upon which these analyses were conducted.

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