Transition of care from adolescence to early adulthood in severe asthmatic patients treated with omalizumab in real life

Received: 5 Dec 2023
Accepted: 8 Feb 2024

To the Editor:

Transitional care consists of managing patients with chronic disease or disability from the paediatric to the adult care system [1–3]. It aims to prepare adolescents to manage their disease to become autonomous young adults, and to avoid any gap in the disease management. To succeed, transitional care must be an integral part of the management, coordinated by the healthcare team [3, 4]. However, the transition period remains critical in current practice, with a risk of loss to follow-up and deterioration in the health of adolescents with chronic conditions [5].

The success of transitional care management in asthma is a major challenge for healthcare systems [3, 4, 6, 7]. With less than a third of asthmatic children remitting during childhood, the adolescent population is particularly concerned by the issue of the transitional care period [4, 8]. Moreover, at that age, rare phenotypes of nonallergic noneosinophilic asthma may appear and make care management even more difficult [9]. If real-life data on transitional care practices are available for other various chronic conditions, they are critically lacking for asthma, and even more so for severely asthmatic adolescents [10]. From a first large-scale study, SOLAIR [11], conducted on asthmatic patients in France from 2009 to 2019 using the French health insurance claim database (Système National des Données de Santé (SNDS)), we explored care pathways in severe asthmatic adolescents treated with omalizumab during the transitional period from 16 to 20 years of age, through the description of healthcare resource use (HCRU).

Optimal matching and classification methods were used to identify clusters of patients with both similar omalizumab exposure patterns and similar transitional care pathways. We performed this advanced clusterisation considering in parallel omalizumab exposure patterns and HCRU of interest. “Care pathway” here includes inpatient and outpatient medical visits with paediatricians and pulmonologists, use of inhaled corticosteroids (ICS) and oral corticosteroids (OCS), hospitalisation for asthma and all-cause hospitalisations. HCRU dissimilarities were assessed per 1-month time sequences, for 48 time-units over the 4-year period (age 16–20 years) using optimal matching. Cluster analysis was performed using unsupervised learning algorithms, based on performance metrics (average silhouette width (ASW), Chi-squared and R^2); the partitioning around medoids method was retained. Differences between clusters for patients’ main characteristics (sociodemographic, adherence to omalizumab and comorbidities) were searched; a significance threshold was set at 0.1 to draw out trends.

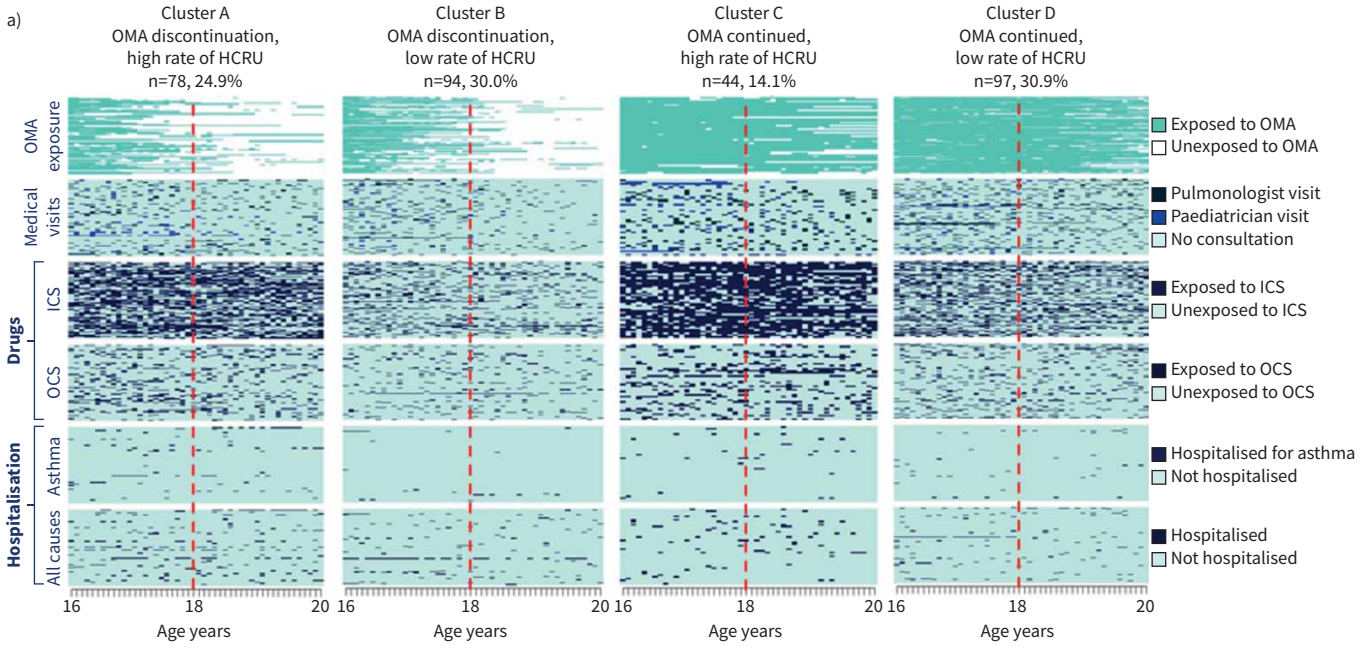
We identified 313 patients who initiated omalizumab before the age of 16 years and were followed-up to 20 years (*i.e.* ⩾4 years of follow-up), and were exposed to omalizumab for ⩾16 weeks (selection criterion of the SOLAIR study). As a reminder, only patients with HCRU markers of asthma were included in the SOLAIR study, notably to exclude the indication of omalizumab for chronic urticaria. Median age at the initiation of omalizumab was 14.0 years (interquartile range 13.0–15.0 years); 59.7% (n=187) of patients were male. One patient died during the 4-year follow-up period (unknown cause).

Four distinct clusters of transitional care pathways were identified (figure 1a). HCRU rates look constant in each cluster throughout the transitional period, with the exception of omalizumab exposure and medical visits with paediatricians who are no longer involved after 18 years.

Shareable abstract (@ERSpublications)
Half of severely asthmatic adolescents treated with omalizumab transitioning to adulthood discontinue the treatment, suggesting insufficient asthma control. However, most of the other half have low rates of HCRU markers, their asthma being under control. https://bit.ly/49ixpxt

Cite this article as: Taillé C, Humbert M, Bourdin A, *et al*. Transition of care from adolescence to early adulthood in severe asthmatic patients treated with omalizumab in real life. *ERJ Open Res* 2024; 10: 00976-2023 [DOI: 10.1183/23120541.00976-2023].

a)



b)

	Cluster A n=78	Cluster B n=94	Cluster C n=44	Cluster D n=97	p-value significance threshold: 0.1
Male	46 (59.0)	65 (69.1)	21 (47.7)	55 (56.7)	0.090
Age at omalizumab intitiation, years	13.0 (12.0–15.0)	14.0 (12.0–14.0)	14.5 (13.0–15.0)	14.0 (13.0–15.0)	0.026
Number of months covered by omalizumab between 16 and 20 years	44.8±3.8	30.3±4.9	16.4±3.8	6.0±3.5	<0.001
Percentage of months covered by omalizumab between 16 and 20 years	93.5±7.9	63.3±10.3	34.1±8.0	12.5±7.4	<0.001
Patients adherent to omalizumab (MPR >80%)	65±83.3	74±78.7	41±93.2	86±88.7	0.094
Comorbidities[#]					
Allergic grounds	56 (71.8)	50 (53.2)	32 (72.7)	67 (69.1)	0.026
Disease of the digestive system	12 (15.4)	7 (7.4)	5 (11.4)	10 (10.3)	NS
Chronic respiratory insufficiency	4 (5.1)	6 (6.4)	3 (6.8)	0 (0.0)	0.033
Obesity	3 (3.8)	3 (3.2)	4 (9.1)	2 (2.1)	NS
Anaphylactic shock[¶]	1 (1.3)	1 (1.1)	0 (0.0)	1 (1.0)	NS
Depressive disorders	1 (1.3)	1 (1.1)	2 (4.5)	2 (2.1)	NS
Malnutrition	1 (1.3)	0 (0.0)	0 (0.0)	1 (1.0)	NS
Urticaria	0 (0.0)	2 (2.1)	0 (0.0)	1 (1.0)	NS
Diabetes	0 (0.0)	1 (1.1)	1 (2.3)	0 (0.0)	NS
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

FIGURE 1 a) Clusters of exposure patterns to omalizumab and healthcare pathway over the adolescent to young adult transition period (age 16–20 years). Index plots represent, per month, omalizumab (OMA) exposure status (exposed/unexposed), medical visit occurrence (visit/no consultation), drug dispensations (yes/no) and hospital stay (yes/no) over the 4-year follow-up period from 16 years to 20 years. Each sequence state is given at the individual level (one continuous line = one patient). The vertical red bar corresponds to the age of 18 years, symbolising the end of childhood. Patients are classified in the same order for each kind of healthcare consumption. For a given month, if patient had visits with both paediatrician and pulmonologist, the pulmonologist was considered for the plot. b) Description of characteristics of adolescents in the four clusters of transitional care pathways. Data are presented as n (%), median (interquartile range) or mean±SD, unless otherwise stated. HCRU: healthcare resource utilisation; ICS: inhaled corticosteroids; OCS: oral corticosteroids; MPR: medication possession ratio. [#]: refer to the SOLAIR source study for comorbidity assessment method using the Système National des Données de Santé [11]; [¶]: allergy diagnosed during hospitalisation, desensitised, tested by patch test, prick test or intradermal reaction, or treated with systemic antihistamines.

Approximately half of the adolescents (n=172, 55.0%) discontinued omalizumab during the transitional period, corresponding to clusters A (n=78, 24.9%) and B (n=94, 30.0%), and most of them discontinued omalizumab before the age of 18 years. Adolescents from cluster A had higher rates of HCRU markers of uncontrolled asthma, suggesting that asthma control would be insufficient. However, it appears that stopping treatment had no impact on HCRU rates for them. Adolescents from cluster B had substantially

lower rates for ICS, OCS and hospital admissions for asthma, markers of asthma that consequently seem to be fairly well controlled. A few assumptions can be made regarding cluster B. This could mean the persistence of a long-lasting effect observed after discontinuation of omalizumab, or even remission of the disease. This has been shown in an observational real-life study in which one in four children successfully achieved omalizumab discontinuation, with no significant difference in asthma outcome when compared to children who continued omalizumab [12]. This again raises the questions of the potential, but never proven, disease-modifying effect of omalizumab, and of how long the treatment duration should last. In addition, adolescents may see their asthma evolve favourably, as shown in the Severe Asthma Research Program cohort, where half of the children with severe asthma no longer had severe asthma after 3 years [13].

The remaining half of the adolescents (n=141, 45.0%), distributed between clusters C (n=44, 14.1%) and D (n=97, 30.9%), gathers those who remained treated with omalizumab during the transitional period. Cluster C, which is the smallest, had markedly higher rates of HCRU markers of uncontrolled asthma while adolescents continued omalizumab (of note, no other biotherapy was available over the study period). Cluster D corresponds to adolescents in whom omalizumab seems to provide benefit with low HCRU while continuing the treatment. In addition, when focusing on adolescents with the lowest HCRU profiles (clusters B and D), HCRU related to asthma (notably the use of ICS) is lower in adolescents from cluster B, *i.e.* those who discontinued omalizumab during the transitional period.

Most patients initiated omalizumab during adolescence. The median age at omalizumab initiation differed significantly between clusters (figure 1b). Adolescents in cluster A, the youngest at initiation, discontinued omalizumab during the transitional period and before 18 years of age, and had high HCRU rates. Male/female ratio also differed significantly. Cluster B (adolescents who discontinued omalizumab before 18 years of age while having the lowest HCRU rates) included the highest proportion of boys (69.1%); cluster C (adolescents who continued omalizumab while having high HCRU rates) included the highest proportion of girls (52.3%). Significant differences were found for adherence to omalizumab, expressed as medication possession ratio (MPR) [11], and assessed during the overall exposure to omalizumab. The lowest proportion of adolescents that were adherent to omalizumab (MPR >80%) was observed for cluster B, while the highest proportion of adherent patients was in cluster C. Lastly, no difference was found among comorbidities, with the exception of the proportion of patients with allergic grounds.

The main limitations of the study have been discussed for the SOLAIR study [11]. One is the absence of clinical data, and details on reasons for medical visits in the SNDS. Therefore, it is not possible to determine reasons for omalizumab discontinuation and whether it was deliberate (*e.g.* lack of efficacy or adverse events, drug discontinuation in patients with prolonged controlled asthma), or otherwise (*e.g.* related to the patients themselves). As its main advantage, the SNDS covers ∼99% of the population in France, allowing the selection of as large as possible, highly representative and unbiased cohorts, and ensures long-term follow-up with very limited loss to follow-up [14]. In addition, the granularity of HCRU in the SNDS allows a detailed analysis of care pathways and of drug exposure based on dispensing data.

To conclude, in this cohort of 313 adolescents with severe asthma treated with omalizumab at the beginning of the transitional period (*i.e.* from adolescence to young adults (16–20 years)), cluster analysis showed that half of them discontinued omalizumab after a long-term treatment, mainly between 16 and 18 years of age, with different trajectories regarding HCRU. Thus, maintenance of omalizumab treatment would not be as regular as expected in adolescents with severe asthma during the transition period, and asthma control would be for some insufficient. Of interest, more than half of children who discontinued omalizumab seemed fairly well controlled after discontinuation, suggesting remission, or overtreatment at omalizumab initiation. More data on asthma course and treatment management during this period are urgently needed.

Camille Taillé[1], Marc Humbert[2], Arnaud Bourdin[3], Céline Thonnelier[4], Audrey Lajoinie[5], Jules Chassetuillier[5], Mathieu Molimard[6] and Antoine Deschildre[7]

[1]Service de pneumologie et Centre de Référence des Maladies Pulmonaires rares, Hôpital Bichat, Groupe Hospitalier Universitaire AP-HP Nord; UMR 1152, Université Paris Cité, Paris, France. [2]Université Paris-Saclay, INSERM, Assistance Publique Hôpitaux de Paris (AP-HP), Service de Pneumologie et Soins Intensifs Respiratoires, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [3]University of Montpellier, INSERM U1046, CNRS UMR 9214, Hôpital Arnaud de Villeneuve, CHU de Montpellier, Hôpital Arnaud-de-Villeneuve, Montpellier, France. [4]Novartis, Rueil Malmaison, France. [5]RCTs, Lyon, France. [6]Service de Pharmacologie Médicale, CHU de Bordeaux, Université de Bordeaux, INSERM

CR1219, Bordeaux, France. [7]Université de Lille, CHU Lille, Pediatric Pulmonology and Allergy Department, Hôpital Jeanne de Flandre, Lille, France.

Corresponding author: Antoine Deschildre (antoine.deschildre@chu-lille.fr)

Provenance: Submitted article, peer reviewed.

Ethics statement: The study was approved by the CNIL (reference number MLD/OTB/AR203292).

Conflict of interest: C. Taillé reports support for the present manuscript from Novartis; and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Chiesi, GSK, Novartis and Sanofi, outside the submitted work. M. Humbert reports support for the present manuscript from Novartis; and consulting fees from AstraZeneca, Chiesi, GSK, Novartis and Sanofi, outside the submitted work, and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, GSK, Novartis and Sanofi, outside the submitted work. A. Bourdin reports support for the present manuscript from Novartis; and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Chiesi, GSK, Novartis and Sanofi, outside the submitted work. C. Thonnelier reports support for the present manuscript from Novartis. A. Lajoinie reports support for the present manuscript from Novartis. J. Chassetuillier reports support for the present manuscript from Novartis. M. Molimard reports support for the present manuscript from Novartis; and consulting fees from Novartis and Stallergen, outside the submitted work; participation on a data safety monitoring board or advisory board for Banook, outside the submitted work. A. Deschildre reports support for the present manuscript from Novartis; grants or contracts from Fondation du Souffle, Conseil Régional Hauts-de-France programme 2014–2018 (grant number ARCiR 2015–284), outside the submitted work; consulting fees from Novartis, ALK, GSK, Sanofi, Aimmune Therapeutics, DBV Technologies, Nestlé Health Science and Boehringer Ingelheim, outside the submitted work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novartis, ALK, GSK, Sanofi, Aimmune Therapeutics, DBV Technologies, Nestlé Health Science and Boehringer Ingelheim, outside the submitted work; support for attending meetings and/or travel from ALK, Sanofi, Boehringer Ingelheim, Stallergenes Greer, Novartis, AstraZeneca, Meda, DBV Technologies, Aimmune and Nutricia, outside the submitted work; and participation on data safety monitoring board for BOOM study (www.ClinicalTrials.gov identifier NCT04045301, Lead Investigator: Philippe Bégin, Montreal), outside the submitted work.

Support statement: This study was supported by Novartis. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Marani H, Fujioka J, Tabatabavakili S, *et al.* Systematic narrative review of pediatric-to-adult care transition models for youth with pediatric-onset chronic conditions. *Child Youth Serv Rev* 2020; 118: 105415.
2 Cassidy M, Doucet S, Luke A, *et al.* Improving the transition from paediatric to adult healthcare: a scoping review on the recommendations of young adults with lived experience. *BMJ Open* 2022; 12: e051314.
3 Roberts G, Vazquez-Ortiz M, Knibb R, *et al.* EAACI Guidelines on the effective transition of adolescents and young adults with allergy and asthma. *Allergy* 2020; 75: 2734–2752.
4 Taillé C, Wanin S, Cros P. Transition dans l'asthme: les clés de la réussite. [Transition in asthma: the keys to success]. *Lett Pneumol* 2021; 6: 274–276.
5 Crowley R, Wolfe I, Lock K, *et al.* Improving the transition between paediatric and adult healthcare: a systematic review. *Arch Dis Child* 2011; 96: 548–553.
6 Deschildre A, Abou-Taam R, Drummond D, *et al.* Mise à jour des recommandations (2021) pour la prise en charge et le suivi des patients asthmatiques adolescents (de 12 ans et plus) sous l'égide de la Société de pneumologie de langue française (SPLF) et de la Société pédiatrique de pneumologie et allergologie (SP2A). Version longue. [Update guidelines for management of asthmatic patients (from 12 years and older). Long version]. *Rev Mal Respir* 2021; 7594: e1.
7 Dufrois C, Bourgoin-Heck M, Lambert N, *et al.* Maintenance of asthma control in adolescents with severe asthma after transitioning to a specialist adult centre: a French cohort experience. *J Asthma Allergy* 2022; 15: 327–340.
8 Wang AL, Datta S, Weiss ST, *et al.* Remission of persistent childhood asthma: early predictors of adult outcomes. *J Allergy Clin Immunol* 2019; 143: 1752–1759.
9 Pijnenburg MW, Fleming L. Advances in understanding and reducing the burden of severe asthma in children. *Lancet Respir Med* 2020; 8: 1032–1044.
10 Worral V, James H, Jones G, *et al.* The development of an asthma transition model from paediatric to adult care. *Eur Respir J* 2019; 54: Suppl. 63, PA928.

11 Humbert M, Bourdin A, Taillé C, *et al.* Real-life omalizumab exposure and discontinuation in a large nationwide population-based study of paediatric and adult asthma patients. *Eur Respir J* 2022; 60: 2103130.
12 Deschildre A, Roussel J, Drumez E, *et al.* Omalizumab discontinuation in children with severe allergic asthma: an observational real-life study. *Allergy* 2019; 74: 999–1003.
13 Ross KR, Gupta R, DeBoer MD, *et al.* Severe asthma during childhood and adolescence: a longitudinal study. *J Allergy Clin Immunol* 2020; 145: 140–146.
14 Tuppin P, Rudant J, Constantinou P, *et al.* Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique* 2017; 65: S149–S167.