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Early View

Research letter

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

Camille Taillé[1], Marc Humbert[2,3,4], Arnaud Bourdin[5], Céline Thonnelier[6], Audrey Lajoinie[7], Jules Chassetuillier[7], Mathieu Molimard[8], Antoine Deschildre[9*]

[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, Le Kremlin-Bicêtre, France ; [3]Assistance Publique Hôpitaux de Paris (AP-HP), Hôpital Bicêtre, Service de Pneumologie et Soins Intensifs Respiratoires, Le Kremlin-Bicêtre, France; [4]Inserm UMR_S999, Le Kremlin-Bicêtre, France ; [5]University of Montpellier, INSERM U1046, CNRS UMR 9214, Hôpital Arnaud de Villeneuve, CHU de Montpellier, Hôpital Arnaud-de-Villeneuve, Montpellier, France; [6]Novartis - Rueil Malmaison, France; [7]RCTs, Lyon, France; [8]Service de Pharmacologie Médicale, CHU de Bordeaux, Université de Bordeaux, INSERM CR1219, Bordeaux, France ; [9]Univ. Lille, CHU Lille, Pediatric Pulmonology and Allergy Department, Hôpital Jeanne de Flandre, Lille, France.

[*]Corresponding author:
Prof. Antoine Deschildre

Transitional care consists of managing patients with chronic disease or disability from the pediatric 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, to date, 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 therefore a major challenge for healthcare systems [3, 4, 6, 7]. With less than a third of asthmatic children who will be in remission 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 non-allergic non-eosinophilic asthma may appear and make care management even more difficult [9]. To date, if real-life data on transitional care practices are available for other various chronic conditions, they are critically lacking for asthma, and even more for severe 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 pathway 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 in- and outpatient medical visits with pediatricians and pulmonologists, use of inhaled corticosteroids (ICS) and oral corticosteroids (OCS), hospitalization for asthma and all-cause hospitalizations. HCRU dissimilarities were assessed per 1-month time sequences, for 48-time units over the 4-year period (16-20 years) using optimal matching. Cluster analysis was performed using unsupervised learning algorithms; based on performance metrics (ASW, CHsq and R2sq), Partitioning Around Medoids (PAM) method was retained. Differences between clusters for patients' main characteristics (sociodemographic, adherence to omalizumab, and comorbidities) were searched; a significance threshold at 0.1 was set to draw out trends.

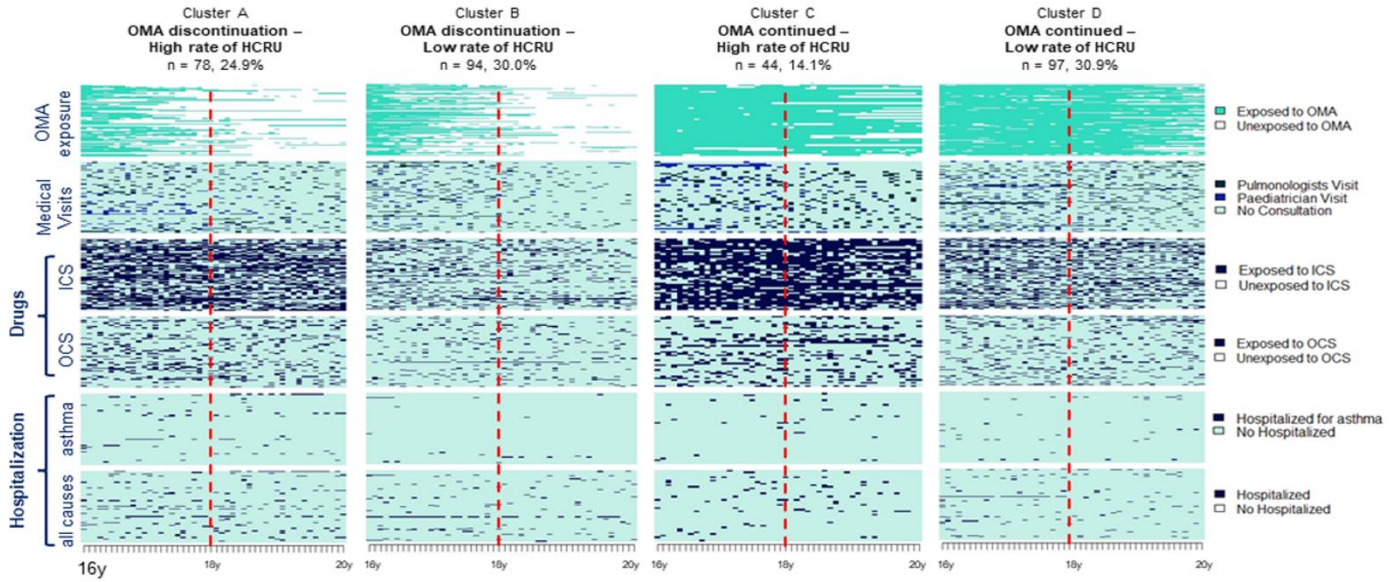
We identified 313 patients who initiated omalizumab before 16 years old and were followed up to 20 years (i.e., at least four years of follow-up), and were exposed to omalizumab for at least 16 weeks (selection criterion of SOLAIR study). As a reminder, only patients with HCRU markers of asthma were included in SOLAIR study, notably to exclude omalizumab indication for chronic urticaria. Median age at the initiation of omalizumab (T_0) was 14.0 years (Q1-Q3: 13.0-15.0); 59.7% were male (n=187). One patient deceased during the 4-year follow-up period (unknown cause).

Four distinct clusters of transitional care pathways were identified (**Error! Reference source not found.**a). HCRU rates look constant per each cluster all over the transitional period, with the exception of omalizumab exposure and medical visits, with pediatricians who are no more involved after 18 years.

Around 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 18 years old. 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 recently 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. Adolescents may also see their asthma evolve favorably, as shown in the Severe Asthma Research Program (SARP) cohort, where half of the children with severe asthma no longer had severe asthma after 3 years [13].

The second half of adolescents (n=141, 45.0%), distributed between clusters C (n=44, 14.1%) and D (n=97, 30.9%), gathers adolescents 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 would correspond to adolescents in which omalizumab seems to provide benefit with low HCRU while continuing the treatment. In addition, when focusing on adolescents with lowest HCRU profiles (clusters B and D), HCRU related to asthma –

notably the use of ICS – visually reaches lower levels in adolescents from cluster B, i.e., who discontinued omalizumab during the transitional period.



Index plots represent, per month, OMA-exposure status (exposed/unexposed), medical visit occurrence (visit/no visit), drug dispensations (yes/no) and hospital stay (yes/no) over the 4-year follow-up period from 16 years to 20 years old. Each sequence state is given at the individual level (one continuous line = one patient). The vertical red bar corresponds to the age of 18, symbolizing 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 pediatrician and pulmonologist: pulmonologist was considered for the plot.

Figure 1a. Clusters of exposure patterns to omalizumab and healthcare pathway over the adolescent to young adult transition period (16-20 years old)

	Cluster A N=78	**Cluster B N=94**	**Cluster C N=44**	**Cluster D N=97**	**p-value** *significance threshold: 0.1*
Male, n (%)	46 (59.0)	65 (69.1)	21 (47.7)	55 (56.7)	p=0.090
Age at omalizumab initiation, median (Q1; Q3)	13.0 (12.0; 15.0)	14.0 (12.0; 14.0)	14.5 (13.0; 15.0)	14.0 (13.0; 15.0)	p=0.026
Number of months covered by omalizumab between 16 and 20 years old, mean (SD)	44.8 (3.8)	30.3 (4.9)	16.4 (3.8)	6.0 (3.5)	p<0.001
Percentage of months covered by omalizumab between 16 and 20 years old, mean (SD)	93.5 (7.9)	63.3 (10.3)	34.1 (8.0)	12.5 (7.4)	p<0.001
Patients adherent to omalizumab (MPR > 80%), n (%)	65 (83.3)	74 (78.7)	41 (93.2)	86 (88.7)	p=0.094
Comorbidities*, n (%)					
Allergic ground	56 (71.8)	50 (53.2)	32 (72.7)	67 (69.1)	p=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)	p=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)	-

*see SOLAIR source study for comorbidity assessment method using the SNDS [11].
**i.e., allergy diagnosed during hospitalization, desensitized, tested by patch test, prick test or intradermal reaction, or treated with systemic antihistamines.

Figure 1b. Description of characteristics of adolescents in the four clusters of transitional care pathways

Most of patients initiated omalizumab during the adolescent age. The median age at omalizumab initiation significantly differed between clusters (Figure 1b). Adolescents of the cluster A, the youngest at initiation, discontinued omalizumab during the transitional period and before 18 years old, and had high HCRU rates. Male/Female (M/F) ratio also significantly differed. Cluster B of adolescents who discontinued omalizumab before 18 y of age while having the lowest HCRU rates gathered the highest proportion of boys (69.1%); cluster C of 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 to the exception of the proportion of patients with allergic ground.

Main limits of the study have been already 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 patient him/herself). Of main advantages, the SNDS covers approximately 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 adolescent age to young adults (16-20 years old) –, 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. Maintenance of omalizumab treatment would thus 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.

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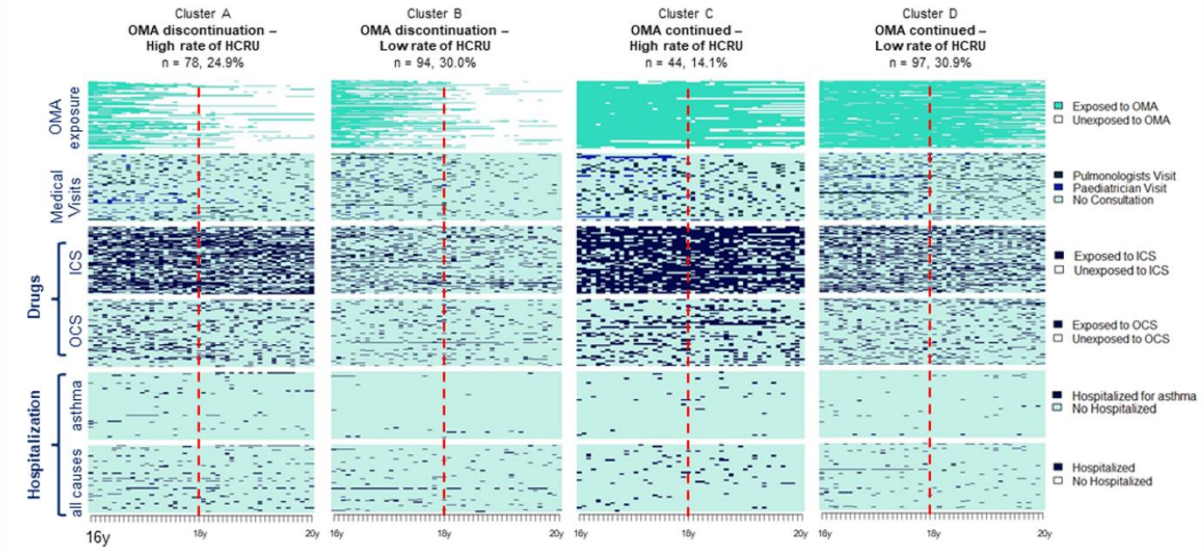

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Figure 1b. Description of characteristics of adolescents in the four clusters of transitional care pathways

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