

10malizumab-assisted desensitization to food in children in real life. A case series.

3Angel Mazon MD PhD<sup>1</sup>, Dah-Tay Jang MD<sup>1</sup>, Begoña Ferrer MD<sup>2</sup>, Sonia Uixera MD<sup>1</sup>,

4Maria Perez-Sabido MD<sup>1</sup>, Laura Ibañez MD<sup>1</sup>, Elisa Buendia MD<sup>1</sup>, Maria Nieto MD<sup>3</sup>,

5Antonio Nieto MD PhD<sup>1</sup>.

71-Unit of Pediatric Allergy and Pneumology. Children's Hospital La Fe. Health

8Research Institute Hospital La Fe. Valencia. Spain.

102-Service of Pediatrics. Children's Hospital La Fe. Valencia. Spain

113-Service of Allergy. University Hospital La Plana, Villarreal, Spain

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16Correspondence: Angel Mazon

17Unit of Pediatric Allergy and Pneumology. Children's Hospital La Fe, Valencia. Spain

18Av. Fernando Abril Martorell 106.

1946026-Valencia, Spain

20+34670342522

21[amazon@comv.es](mailto:amazon@comv.es)

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33To the Editor,

34Desensitization (DSZ) or induction of oral tolerance has changed the management of

35food allergy, but it is not free of risks, with frequent reactions, especially in those with

36severe allergy.<sup>1</sup> Omalizumab (OMZ) has been used to improve safety and shorten the

37procedure.<sup>2,3</sup> We published the first report on the recurrence of symptoms after

38discontinuing the drug in three children who had been desensitized while receiving

39OMZ.<sup>4</sup> We now report the clinical results of this approach, in real life conditions, in a

40larger series of children with high risk allergy, with longer follow-up periods.

41We describe 21 patients (three from the initial report) with allergy to cow's milk (11) or

42hen's egg (10), who had had severe reactions. Data are shown in table 1 and figure 1. A

43procedure of DSZ without OMZ had previously failed in thirteen patients; it was used in

44the other eight as symptoms were anticipated due to severity of their condition. One

45patient was already receiving OMZ for more than two years for severe asthma; twenty

46received OMZ as an off-label use with informed consent from parents.

47We planned to administer OMZ during at least 2-3 months, then perform DSZ while

48patients were on OMZ and keep this at least 2-3 months after reaching the target dose of

49200 mL of milk (6 gr protein) or 35 mL of raw egg white (3.8 gr protein). We used the

50DSZ protocol of the Spanish Society of Pediatric Allergy, Asthma and Clinical

51Immunology (SEICAAP),<sup>5</sup> individually adapted according to reactions and individual

52needs. Once the target was reached, patients were instructed to have 200 mL of milk

53twice a day or an egg omelet (or equivalent) three times a week.

54The patients received OMZ during periods of two months to 2.1 years prior to starting  
55DSZ. The procedure of DSZ took between one and nine months.

56DSZ was abandoned in two patients: the one (#1) with severe asthma (before reaching  
57the target) due to worsening asthma that could be caused by milk, and another (#2) for  
58developing severe digestive symptoms shortly after reaching 200 mL of milk,  
59symptoms that persisted despite progressively decreasing the amount until milk was  
60finally withdrawn. The procedure initially failed in another patient (#3), who presented  
61severe and repeated vomiting with very small amounts of egg white.

6218 patients reached the target dose, and OMZ was discontinued 18 days to 1.6 years  
63later in 17 patients. The other (#4) is still on OMZ and having milk after 4.6 years, as he  
64initially had 2040 kU/L of casein specific IgE and it was considered too risky to stop  
65OMZ. Last levels were 389 kU/L after 3.9 years.

66Eight of the 17 patients (#5 to #12) continue to tolerate the food, which they take  
67regularly 1.2 to 7 years since OMZ was stopped; three of them presented some transient  
68minor symptoms.

69One of the 17 patients (#13) presented minor symptoms three months after stopping  
70OMZ; she was very reluctant to take egg and decided to quit the procedure.

71The other eight patients (#14 to #21) also presented symptoms with the food they were  
72taking regularly 1.5 to 6 months after stopping OMZ. The symptoms were mainly  
73vomits, which precluded the continuation of DSZ, or even anaphylactic reactions. The  
74symptoms reappeared in challenges performed at our hospital to confirm causality in  
75five patients; in the others causality was assumed due to a clear history and accumulated  
76experience in previous patients.

77OMZ was resumed in these eight patients as well as in patient #3 (n=9) and after one  
78day to 5.5 months of treatment six patients underwent a new rush procedure of DSZ and

79three a direct challenge test with the food. All tolerated the food and continued to take it  
80regularly; OMZ was again discontinued in them 0.7 to 1.2 years later.

81Six of the nine patients (#14 to #19) are currently taking regularly the food 1.3 to 5.1  
82years after the second cycle of OMZ was finished. Patient #3 started to present minor  
83symptoms and decided to quit. The other two patients (#20 and #21) again presented  
84symptoms 3 and 8 months after the second cycle of OMZ was stopped and decided to  
85quit the procedure.

86Reports on OMZ-assisted DSZ (varied in terms of administration) have not found  
87important differences in children without high risk, who usually tolerate well the  
88procedure.<sup>6</sup> Those with high risk have been able to reach the target in 75 - 100% of  
89cases.<sup>7</sup> Generally the follow-up time has not been long; challenges have been performed  
9012 weeks after discontinuing OMZ, with 43% of patients failing to pass.<sup>8</sup>

91This report is not a controlled trial, useful to learn about mechanisms<sup>9</sup> or factors  
92predicting failure/success, but a descriptive study on the evolution of patients in real life  
93conditions. Thus there was a large variation in the duration of treatment and in the  
94procedure itself, adapted to individual needs (availability for visits, distance to the  
95hospital) and to ongoing accumulated experience. When a new cycle of OMZ was used,  
96patients tolerated a rush DSZ procedure or even a direct challenge and could resume  
97ingestion of the food. We had a more conservative and slow approach in the first  
98patients, and gradually shortened or even suppressed the period of avoidance of the food  
99between the cycles of OMZ in the subsequent patients. We found, for clinical practice  
100and information of patients, that OMZ-assisted DSZ failed in six (28%) of patients with  
101high risk, even after a second cycle of OMA, specially for egg; eight (38%) patients  
102were able to tolerate the food after one cycle of OMZ, six (28%) needed a second cycle  
103of treatment of one year, and it is soon to assess response in another one. Information  
104about results must be provided to patients and parents before performing this procedure,

105especially for older children and adolescents. Commitment is important as much  
106dedication and effort are needed and failure is not infrequent, even in patients with not  
107too high specific IgE levels. Also, our findings suggest that a period of 12 weeks after  
108stopping OMZ is too short to ensure continuing tolerance, and that longer intervals, at  
109least four or rather six months, would be necessary before diagnosing tolerance or  
110sustained unresponsiveness as opposed to desensitization or temporary  
111hyporesponsiveness.

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113Angel Mazon MD PhD<sup>1</sup>, Dah-Tay Jang MD<sup>1</sup>, Begoña Ferrer MD<sup>2</sup>, Sonia Uixera MD<sup>1</sup>,  
114Maria Perez-Sabido MD<sup>1</sup>, Laura Ibañez MD<sup>1</sup>, Elisa Buendia MD<sup>1</sup>, Maria Nieto MD<sup>3</sup>,  
115Antonio Nieto MD PhD<sup>1</sup>.

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1171-Unit of Pediatric Allergy and Pneumology. Children's Hospital La Fe. Health  
118Research Institute Hospital La Fe. Valencia. Spain.

119

1202-Service of Pediatrics. Children's Hospital La Fe. Valencia. Spain

1213-Service of Allergy. University Hospital La Plana, Villarreal, Spain

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163Legend of figure

164Figure 1: Schematic chronology of administration of omalizumab (OMZ), build-up  
165phase of desensitization (DSZ), ingestion of the food and appearance of symptoms. The  
166length of bars is not proportional since there was a large variation of periods from  
167patient to patient.

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