

Refractory insulin allergy: pancreas transplantation or immunosuppressive therapy alone?

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Recently, Yonk *et al.* [1] described the sequential use of two targeted biologic agents – rituximab and omalizumab along with corticosteroids to treat a patient with severe systemic insulin allergy accompanied by marked metabolic dysregulation and corticosteroid toxicity.

In 1996, a 50-year-old woman was diagnosed with type 1 diabetes mellitus (DM). Shortly after initiation of insulin therapy, a general urticarial rash resulting in excoriation, bleeding and disrupted sleep occurred. Prednisolone alone provided symptomatic relief until 2003 when corticosteroid-related complications were reported including high glycated haemoglobin levels (11.3%), weight gain, memory impairment and osteoporosis. Therefore, a more aggressive treatment was proposed with azathioprine, then methotrexate and eventually, rituximab, mycophenolate mofetil and omalizumab along with a continuing but decreasing dose of prednisolone. Unbearable symptoms ceased only with omalizumab therapy. Therefore, Yonk *et al.* [1] claimed that although combined therapy is relatively expensive, it was more economical and safer than pancreatic transplantation alone (PTA) which we proposed in one young patient with life-threatening severe insulin allergy.

Indeed, in 2006, we reported in the present Journal [2] on a 30-year-old man, with type 1 DM, who developed generalized allergy to insulin consisting of several bouts of tremor, tachycardia, breathlessness and syncope with strong positive reactions to protamine and metacresol. He underwent a PTA with portal-enteric drainage in June 2003. Following the antithymocyte globulin induction, immunosuppression consisted in tacrolimus and sirolimus without steroids. Currently, 6 years after transplantation, the patient is euglycaemic without exogenous insulin

therapy (glycated haemoglobin 5.8%) and free of allergic reactions. He is totally rehabilitated with a full-time job.

Yonk *et al.* [1] claimed the benefit of using omalizumab, an anti-IgE mAb which was approved by the US FDA for persistent allergic asthma. This recombinant humanized mAb is supposed to block free serum IgE and prevents IgE-mediated inflammatory changes. Anaphylaxis was reported in about 0.2% of patients, and the most frequent side-effects were injection-site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%). A possible increase in the rate of cardiovascular events requires further evaluation.

Reports on two patients were previously published: in 2007, Matheu *et al.* [3] presented a successful case in a 27-year-old man with DM but in 2008, Wong [4] did not succeed in a 55-year-old man with steroid-dependent asthma and had to change the insulin type, despite concomitant use of omalizumab.

Although morbidity remains a serious concern, for selected young recipients with insulin allergy, we think that PTA is still a valid, long-term, cost-effective option [5,6]. For our 30-year-old PTA recipient [2], the medical costs were estimated at 25 428 € (transplantation) and less thereafter (Table 1) by his insurance company. The annual cost of omalizumab, for treatment of allergic asthma, varies from 10 000 to 15 000 €, and mycophenolate mofetil, from 1975 to 3950 €, while rituximab costs 1310 € per vial of 500 mg.

Moreover, PTA offers insulin independence, improves metabolic control and prevents progression of secondary diabetic complications [5,6]. The price to pay for both therapies is the long-term exposure to immunosuppressive drugs.

Table 1. Yearly total cost (in Euros) for our PTA recipient transplanted on June 22, 2003, including total hospital costs, medical honorarium, drugs administrated during hospitalization and daily immunosuppressive therapy.

Year	2003	2004	2005	2006	2007	2008
Inpatient care and Medical Honorarium	19 141.36	6975.85	4837.14	2790.34	2270.71	4821.98
Inpatient drugs costs	6287.03	517.32	210.66	323.38	0	28.59
Outpatient drugs costs	17 447.30	17 091.29	9045.52	8808.08	9654.75	6592.56
Total	42 875.69	24 584.46	14 093.32	11 921.80	11 925.46	11 443.13

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Jacqueline Léonet,¹ Jacques Malaise² and
Jean-Paul Squifflet³

¹ CHPLT, rue du Parc, Verviers, Belgium

² Hôpital Notre-Dame, Centre Hospitalier de l'Université
de Montréal, Montreal, QC, Canada

³ Department of Abdominal Surgery and Transplantation,
University of Liège, Liège, Belgium

References

1. Yonk PFK, Malik R, Arif S, *et al.* Rituximab and omalizumab in severe, refractory insulin allergy. *N Engl J Med* 2009; **360**: 1045.
2. Léonet J, Malaise J, Goffin E, *et al.* Solitary pancreas transplantation for life-threatening allergy to human insulin. *Transpl Int* 2006; **19**: 474.
3. Matheu V, Franco A, Perez E, Hernandez M, Barrios Y. Omalizumab for drug allergy. *J Allergy Clin Immunol* 2007; **120**: 1471.
4. Wong S. Exacerbation of asthma after initiation of insulin therapy in a patient treated with Omalizumab. *Ann Allergy Asthma Immunol* 2009; **102**(Suppl.): A78.
5. Gruessner RW, Sutherland DER, Gruessner AC. Mortality assessment for pancreas transplants. *Am J Transplant* 2004; **12**: 2018.
6. Gruessner RW, Sutherland DER, Gruessner AC. Survival after pancreas transplantation. *JAMA* 2005; **293**: 675.