ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Research letter

The six million dollar man

Mathilde Volpato, Stefan Nowak, Jean Luc Bourrain, Pascal Demoly, Engi Ahmed, Arnaud Bourdin, Jeremy Charriot

Please cite this article as: Volpato M, Nowak S, Bourrain JL, *et al*. The six million dollar man. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00341-2020).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Copyright ©ERS 2020. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

The six million dollar man

Mathilde Volpato[1], Stefan Nowak[1], Jean Luc Bourrain[1], Pascal Demoly[1], Engi Ahmed[1], Arnaud
Bourdin[1] and Jeremy Charriot[1]

1. Department of Respiratory Diseases, University of Montpellier, Montpellier, France.

Correspondence to
Pr Arnaud Bourdin
Department of Respiratory Diseases
Hopital Arnaud de Villeneuve
CHU Montpellier
Montpellier
France
a-bourdin@chu-montpellier.fr

The patient gave oral and written consent for this clinical communication.

To the editor,

We report here the observation of a sixty-year-old male, jeweler, suffering from severe asthma. Asthma onset was reported by age 30. The patient also reported comorbid severe chronic rhinosinusitis with nasal polyposis since adolescence. Aspirin and NSAIDs intolerance were considered to worsen asthma symptoms since one clear episode of emergency room attendance rapidly after aspirin ingestion. Episodes of generalized chronic urticaria have led to genuine anaphylactic reactions treated with epinephrine twice in the past but fortunately with no needs for orotracheal intubation. No trigger for these episodes could be identified despite appropriate provocation tests.

Recombinant anti-immunoglobulin E antibody (Omalizumab) was initiated in 2006 and continued until 2015 because his asthma was uncontrolled despite being managed according to GINA: he presented at least five exacerbations the year before requiring high doses of systemic corticosteroids and he was eligible to the drug as he had known perennial sensitizations (house dust mite, cypress pollens, etc…) and an elevated serum total IgE level (739 kU/L). Oral corticosteroids (OCS) maintenance was established at 20 mg/day.
During the first years of treatment with omalizumab the number of exacerbations were reduced and the control of asthma was improved.
Progressive tapering of maintenance dose of OCS could be achieved down to 10 mg per day, but complete weaning was unsuccessful due to asthma relapse.
After the good initial response to omalizumab, exacerbation outbreak and mitigate control of asthma made us think about alternative therapies (figure 1). The eosinophil blood count at that time was at 1640 per mm3, without argument for neither ANCA-associated vasculitis nor bronchopulmonary aspergillosis based on dedicated examinations including chest CT scan and auto-immunity assessment. The inhaled treatment observance was good and included a maintenance and reliever therapy with a fixed combination of ICS (1500 BDP) - LABA and a LAMA. FEV1 was 67% of predicted value (June 2015).

The opportunity to benefit from another immunotherapy with anti-IL5R monoclonal antibody in a clinical trial (i.e. the ZONDA trial at that time) suggested the suspension of Omalizumab then a washout time of at least four months.
Two and three months after omalizumab withdrawal, he presented on two occasions at the emergency department for documented anaphylactic shocks that required parenteral steroids use at 2 mg/kg for 3 consecutive days. No convincing triggering factor could be identified. On the other hand, asthma remained relatively unaffected by the withdrawal of omalizumab in terms of control of symptoms, exacerbation rates and lung function.
Considering the vital risk related to these anaphylactic shocks, we introduced another biologic, an anti-IL-5 monoclonal antibodies (Mepolizumab) as part of the registered temporary authorization utilization (TAU) before ZONDA inclusion criteria could be completed, in December 2015. After five injections of this monoclonal antibody (mAb), whereas the daily dose of OCS could be progressively tapered as the level of asthma control was continuously improving (of note, FEV1 was then at 73% of predicted value), he continued to suffer from episodes of giant urticaria despite a regularly observed treatment with fexofenadine hydrochloride with another emergency admission for angioedema requiring a novel burst of OCS.
After multidisciplinary concertation meeting, we decided to introduce Omalizumab as a concomitant biologic treatment at a dose regimen of 300 mg every four weeks as indicated for chronic idiopathic urticaria because of the absence of any anaphylactic shock during previous treatment with Omalizumab.
Since that time, he receives a monthly injection of both Mepolizumab and Omalizumab on the same day in different shoulders.

Nowadays, this patient is totally weaned from oral glucocorticoids, with a controlled asthma and a stable lung function with FEV1 at 2.71 L (86% of predicted value) for a FVC at 4.11L (103% of predicted value). He no longer declares any skin itching or anaphylactic manifestation. He hasn't been hospitalized or admitted to emergency department. He doesn't use anymore his reliever therapy, stopped his LAMA therapy and reduced the daily dose of ICS to 1000 µg/d. He had only one mild exacerbation (probable viral trigger), treated with oral corticosteroids for 5 days at 0.5 mg / Kg during the past three years of follow up. The troublesome symptoms of rhinosinusitis are still at the forefront.

Discussion:
The use of monoclonal antibodies in asthma is based on the understanding of T2 pathophysiological mechanisms. Currently, the choice between those directed against IL-5 or IgE is relatively insoluble in
patients who are eligible for both, which was and still is the case for this patient [1]. Combining biologics for treating partially responding severe asthmatics is an attractive option but to date it was not assessed likely because of concerns related to costs, as mentioned by the provocative title. Interestingly, this patient presents a relatively clear-cut symptomatology with not overlapping mechanisms despite being all situated under the T2 umbrella; he seems to have an IgE's dependence for urticaria and anaphylactic manifestations considering the good response to Omalizumab on this point, especially since these manifestations relapsed during this drug's withdrawal. On another side, he seems to have an IL5-driven asthma as there is a certain connection between the elevated eosinophilic blood count, cortico-dependency, respiratory symptoms and the rhinosinusitis manifestations, and the beautiful response to mepolizumab.
We acknowledge these elements are mostly clinical and therefore subject to discussion in particular on the symptom's subjectivity, their relatively low specificity, the very long disease evolution and some reported difficulty to establish a clear clinical distinction between the two. The vital risk and the unacceptable side effects of systemic corticosteroids have prompted us to propose this exceptional management but raised an issue not tackled until today. This patient's profile therefore corresponds to both biologics approval because Omalizumab is also approved in chronic urticaria, when resistant to conventional treatment guideline [2]. In addition, the switch of this dual-therapy to dupilumab, an anti-IL4/IL13 monoclonal antibody, could reasonably be considered as evidence of benefits are clear either in severe asthma and in chronic urticaria [3]. The quite high blood eosinophil count recorded before mepolizumab start (1640/mm3) might be the only limit as there are no data in this range, patients with counts higher than 1500/mm3 having been excluded from the RCT [4, 5].

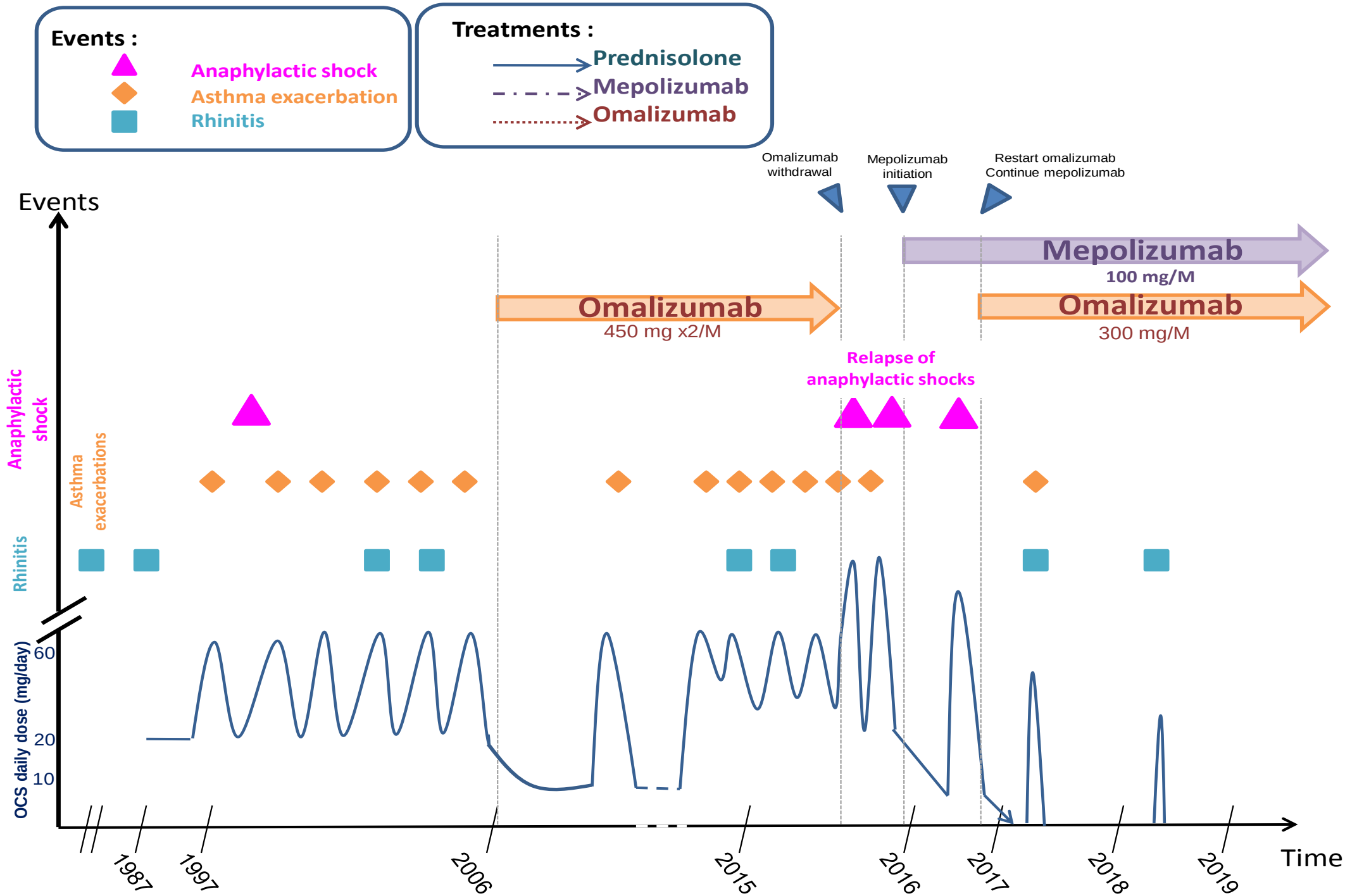
1. Bousquet J, Brusselle G, Buhl R, Busse WW, Cruz AA, Djukanovic R, Domingo C, Hanania NA, Humbert M, Gow AM, Phipatanakul W, Wahn U, Wechsler ME. Care pathways for the selection of a biologic in severe asthma. *European Respiratory Journal* [Internet] 2017 [cited 2020 Aug 7]; 50Available from: https://erj.ersjournals.com/content/50/6/1701782.

2. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Katelaris CH, Kocatürk E, Kulthanan K, Larenas-Linnemann D, Leslie TA, Magerl M, et al. The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018; 73: 1393–1414.

3. Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. *The Journal of Allergy and Clinical Immunology: In Practice* 2019; 7: 1659-1661.e1.

4. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martincova R, Graham NMH, Hamilton JD, Swanson BN, Stahl N, Yancopoulos GD, Teper A. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *New England Journal of Medicine* 2018; 378: 2486–2496.

5. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A, Chao J, Staudinger H, Pirozzi G, Antoni C, Amin N, Ruddy M, Akinlade B, Graham NMH, Stahl N, Yancopoulos GD, Teper A. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *New England Journal of Medicine* 2018; 378: 2475–2485.


Events :
Anaphylactic shock
Asthma exacerbation
Rhinitis
Treatments :
Prednisolone
Mepolizumab
Omalizumab
Omalizumab withdrawal
Mepolizumab initiation
Restart omalizumab
Continue mepolizumab
Events
Mepolizumab
100 mg/M
Omalizumab
450 mg x2/M
Omalizumab
300 mg/M
Relapse of anaphylactic shocks
Anaphylactic shock
Asthma exacerbations
Rhinitis
OCS daily dose (mg/day)
60
20
10
1987
1997
2006
2015
2016
2017
2018
2019
Time