Adjuvant use of Omalizumab in Beta-Lactam Desensitisation

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Case Report

We present a case of a 43 year old female with history of anaphylaxis to penicillin and multiple comorbidities who was desensitised to Pivmecillinam (penicillin) aided by adjuvant Omalizumab.

43 year old wheelchair bound female with supra pubic catheter and recurrent UTIs was referred to our drug allergy unit for assessment of penicillin allergy. She reported history of vomiting, severe difficulty in breathing, swollen lips, and cardiovascular collapse following administration of non-further specified penicillin over 20 years ago.

Her medical history included severe post-traumatic stress disorder, pulmonary embolism, ileostomy, chronic pelvic pain and peripheral nerve damage with an atomic bladder. In the last year, she had multiple hospital readmissions with urinary tract sepsis with bacteraemia. All surgical options for improving urinary flow had been fully explored and considered too high risk at this stage.

Patient’s total IgE measured 137, specific IgE was negative (Penicilloy G - 0.06, Penicilloy V - 0.02, Amoxycilloyl - 0.04). We performed standard skin testing with penicillin allergy determinants: penicillloy poly-L-lysine (PPL), minor determinant mixture (MDM) (Diater Laboratory, Madrid, Spain), benzylpenicillin, amoxicillin, clavulanic acid as well as Cefuroxime. Patient tested positive to PPL and Aminocillin at 1:10 as well as Cefuroxime (2.5 mg/mL) intradermal skin testing. She tested negative to MDM, Benzylpenicillin and Clavulanic Acid at intradermal testing 1:10. In view of positive test results further testing was not performed. During skin testing patient developed generalised flushing, itching and nausea, her observations were stable and she was treated with antihistamine only. A recommendation of penicillin and cephalosporin avoidance was made. In preparation for future intravenous therapy if required, she re-attended for carbapenem/ penicillin cross reactivity assessment. Meropenem skin testing was negative (skin prick test and intradermal test at 5 mg/mL). Patient was challenged with iv meropenem and tolerated full therapeutic dose of 1000 mg. Soon thereafter she was admitted with a resistant Klebsiella urinary tract infection with sepsis and Meropenem intravenous therapy was instituted, although subsequently discontinued due to likely meropenem associated liver toxicity (raised LFTs and normal liver ultrasound). In view of her ongoing risk of recurrent UTIs with significant sepsis, increasing isolates of drug resistant bacteria, and associated failure of previous antibiotic prophylaxis strategies a multidisciplinary (Allergy /Infectious Diseases) decision was made to desensitise her to Pivmecillinam (a 1st line antibiotic for UTI in some EU countries, to which the patient’s recent isolates had maintained sensitivity). Considering her multiple comorbidities Omalizumab was recommended as adjuvant therapy.

Patient signed informed consent to Pivmecillinam desensitisation with adjuvant use of Omalizumab. Omalizumab 300 mg sq was administered 72 hours prior to the desensitisation. Her repeat PPL skin testing 24 hours post Omalizumab was positive (Amoxicillin was not retested). Pivmecillinam desensitisation was performed in an acute medical ward with one to one monitoring by consultant allergist and senior allergy nurse. Continuous cardiac monitoring and regular (every 15 minutes) observations were instituted. She underwent 20 steps rapid oral Pivmecillinam desensitisation (Table 1.) Cetirizine 10 mg po and Hydrocortisone 100 mg IV were used for premedication. This was tolerated well, except for central chest pain at step 16. Other than mild tachycardia (80 – 90 bpm) there were no ECG changes. She was managed with oral Ranitidine 150 mg. Patient achieved cumulative loading dose of 508 mg of Pivmecillinam and subsequently received daily Pivmecillinam 100 mg TDS for the next 9 months. Omalizumab treatment was not repeated and tolerance was maintained by continuous meticulous treatment with Pivmecillinam. Although frequency of UTIs was reduced, she eventually underwent cystectomy and formation of an ileal conduit 9 months later and the pivmecillinam was discontinued.

Discussion

Drug desensitisation may be considered in cases where there are no other suitable drug alternatives or when potential alternatives have inferior efficacy. Omalizumab has been shown to prevent anaphylaxis in high-risk desensitisations, in wasp and bee venom immunotherapy, ragweed rush immunotherapy as well as milk and oxaliplatin desensitisation [1-5]. Administration of Omalizumab results in a rapid reduction of free IgE level within 1 to 2 hours in serum, averaging an 84–99% reduction relative to baseline [6]. This in time leads to the downregulation of FceRI on mast cells/basophils [7]. Although, IgE suppression is slowly and completely reversible upon withdrawal of Omalizumab therapy, there are no signs of rebound, which makes it an ideal adjuvant agent in high risk desensitisations [8].

Pivmecillinam was considered as long term prophylactic antibiotic for this patient based on antibiotic sensitivities and its good safety profile. Pivmecillinam is a unique beta-lactam antibiotic for the treatment of UTIs. It has selective activity against Gram-negative bacteria, especially E. coli, the bacterium most commonly responsible...
for UTI. Standard treatment regimens (200-400mg tds) have bacteriological cure rates of 90% or above and the clinical outcomes are consistent with bacteriological outcome [9]. Pivmecillinam is the pro-drug of mecillinam, chemically it is the pivaloyloxymethylester of the amidinopenicillanic acid, mecillinam. Its serum half-life is 1.2 hours and the protein binding amounts to 5-10%. Approximately 50% of the administered dose is excreted as mecillinam in the urine within the first six hours [10]. These drug characteristics (short half-life and low protein binding) point towards a TDS, rather than BD, post desensitisation drug maintenance regime.

Omalizumab was considered as adjuvant treatment in this case, because of the patient’s comorbidities, previous history of grade 3 anaphylaxis with penicillin, and systemic symptoms during skin testing [11].

Our patient, who at the time was both physically and mentally frail, tolerated Pivmecillinam desensitisation and the subsequent Pivmecillinam treatment very well. It is possible that she would have tolerated it irrespective of adjuvant Omalizumab, however, it was felt that this protocol offered additional “safety net”.

In conclusion, we have described a successful, safe Pivmecillinam rapid drug desensitisation (RDD) with adjuvant Omalizumab in a patient with multiple comorbidities and history of penicillin anaphylaxis. RDD induces temporary tolerance to a drug, allowing a medication allergic patient to receive the optimal agent for his or her disease [12]. However, despite its clinical efficacy and tolerogenic effects, the use of RDD has been limited by the potential for serious allergic reactions, including anaphylaxis. RDD protocols with adjuvant Omalizumab such as the one described here, permit patients, who otherwise would have been considered too high risk for drug desensitisation, to continue safely with first-choice therapies, leading to improved prognosis and better treatment outcomes.

References
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