

A SOUTH AFRICAN MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC

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ABSTRACT

Immune function is not limited to a particular organ system and neither is immune-mediated pathology. Drug hypersensitivity reactions, having a diversity of pathophysiologic mechanisms, manifest with a range of clinical disorders. A particular drug can cause varied immune-based pathology in different individuals and to varying extents in the context of co-morbid diseases such as HIV. Consequently, a range of specialists care for the different reactions caused by a single drug. This may limit our ability to detect common clinical features and uncover unifying immunopathogenesis linked by the pharmacology of the particular offending drug. Furthermore, in South Africa with the ongoing TB/HIV epidemics, drug hypersensitivity reactions are common, occur in the context of polypharmacy and concomitant systems pathology and frequently require multidisciplinary input for optimal care within the constraints of limited therapeutic alternatives. To address this problem and in line with the global trend towards systems biology and personalised medicine, a multidisciplinary drug hypersensitivity clinic at Groote Schuur Hospital has recently been started – the first of its kind in South Africa. This article outlines the background to the formation of this initiative, the potential advantages and needs of a multidisciplinary drug hypersensitivity clinic and the focal starting point of this clinic to better understand the spectrum of immune-based hypersensitivity reactions to Rifampicin.

INTRODUCTION

South Africa, as one of the BRICS emerging national economies, is facing a health transition. Health systems remain burdened by the HIV and TB epidemics, yet non-communicable diseases are rising.¹ Prescribing practices, although still dominated by anti-retroviral and anti-tuberculous medicines, continue to expand to include an ever-increasing list of relevant chronic medications as well as novel small molecule and biologic therapies. Clinicians, already battling to keep up with the uses and predictable type A side-effects of this expanding medicinal armamentarium, need to be supported in managing the idiosyncratic Type B drug reactions. Many of these reactions are life-threatening with the majority being immune-mediated. In the context of HIV and TB, many occur in patients with multi-system co-morbidities and polypharmacy, thus requiring care from different sub-specialists. In addition, a cross-disciplinary effort is required to adequately surveil, respond, manage and research the patterns and dominant offending drugs within our local populations. It is out of this background that a multidisciplinary drug hypersensitivity clinic at Cape Town's Groote Schuur Hospital has been formed – a first for South

Africa. In this brief review the rationale for the formation of this initiative will be outlined. The potential advantages and needs of a clinic of this nature will be discussed utilising as a focal starting point the spectrum of immune-based hypersensitivity reactions to rifampicin.

WHY A MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC?

There are two main drivers behind the formation of this multidisciplinary drug hypersensitivity clinic:

- I. A drug rather than clinical phenotype/organ-system focus; and
- II. The complexity of patients with drug hypersensitivity reactions in South Africa.

A single drug can cause different immune-mediated drug hypersensitivity reactions (DHR) (Figure 1). For instance, beta-lactam antibiotics can cause urticaria, angioedema and anaphylaxis through an IgE-mediated type 1 reaction, leucocytoclastic vasculitis and serum sickness through an immune-complex type III reaction and a maculopapular rash and even a severe cutaneous adverse reaction

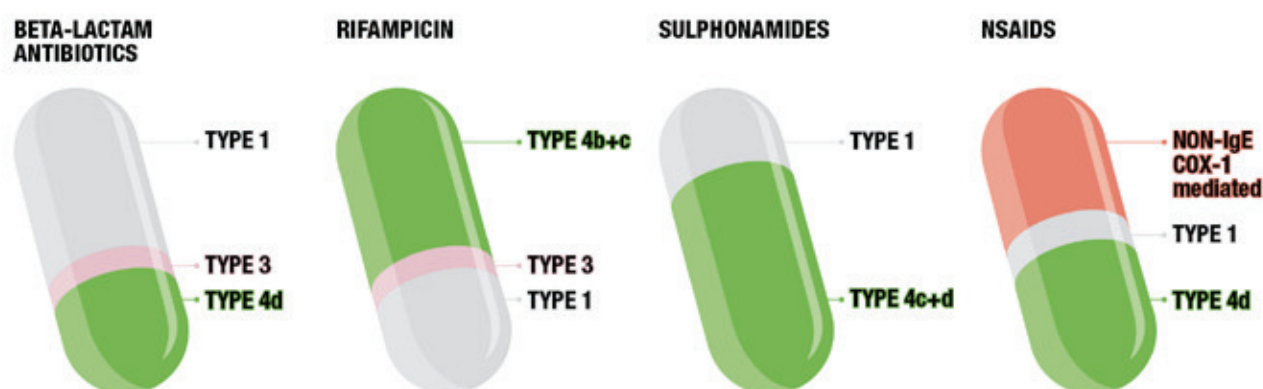


Figure 1: Drugs causing different types of immune-mediated pathology

(SCAR) via a T-cell mediated type IV reaction.² Currently, a patient with this spectrum of reactions would see an allergist, a rheumatologist, and a dermatologist with no required communication between them. This is an opportunity lost. In many instances the approach has been to blame a chemical without understanding that host factors may contribute as the underlining and perhaps unifying aetiology of these clinically diverse reactions. Important host factors may relate to pharmacogenomics, immunology or target organ susceptibility.

We have entered the era of systems biology. This is beginning to highlight the limitations of artificial clinical phenotypes. The move is towards phenotyping based on pathophysiological mechanisms. The immune system and its' pathologies, without a well-defined organ 'home' certainly lend themselves better to these mechanistic approaches. Thus, it is logical that a multidisciplinary drug hypersensitivity clinic, seeing the entire spectrum of

a particular drug's immune-mediated reactions, will offer new insights and allow mechanistic approaches to best applied.

Readers are encouraged for further illustrative examples and a more in-depth review of immune-mediated drug hypersensitivity in South Africa to refer to our article on this topic in the last edition of *Current Allergy and Clinical Immunology*.³

The most severe forms of SCAR are toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS) with mortality over 35% and 10% respectively.^{4,5} In the South African context, these most commonly occur secondary to nevirapine, cotrimoxazole and rifampicin usually in patients with HIV infection, advanced immunosuppression and disseminated TB.⁶⁻⁸ These patients are often taking at least seven drugs at the time of their reactions and frequently have both TB and additional opportunistic infections. The natural history of TEN and DRESS can lead to the development of sepsis and liver/renal impairment or failure. The patient's nutritional, fluid and skin care requirements often need daily specialised attention. Thus, the optimal care of these patients requires input from multiple specialities - dermatology, intensive care, infectious diseases, hepatology, nephrology, nursing and dietetics. Identifying the offending drug/s requires admission and substantial resources and expertise, especially in the context of either sub-optimal or no available *in vivo* or *in vitro* tests. Consequently, the day-to-day care of these complex drug hypersensitivity reactions encourages multi-disciplinary care team collaboration. Added to this, there is a spectrum of less severe drug hypersensitivity reactions that should be able to access and benefit from multi-disciplinary outpatient services.

STRUCTURE AND NEEDS OF THE MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC

The drug hypersensitivity clinic will be staffed by specialists and trainee specialists including allergologists,

TABLE I: REQUIREMENTS FOR AN OPTIMAL FUNCTIONING MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC AND PLATFORM

PHYSICAL INFRASTRUCTURE:

1. Clinic
 - a. Consultation rooms;
 - b. Refrigeration for storage of skin/intradermal/patch drugs (4 degree);
 - c. Consumables for patch testing, e.g. Finn Chambers;
 - d. Photo patch testing equipment;
 - e. Resuscitation equipment to treat anaphylaxis;
 - f. Computing equipment required for admin and data capture.
2. Laboratory
 - a. Centrifuge, sterile hood for processing human blood and tissue;
 - b. -20 and -80 degree storage facility;
 - c. Access to specialised equipment facilities including flow cytometer, ELISA readers, tissue culture facilities and luminex.

HUMAN RESOURCES:

1. Clinic
 - a. Specialist clinicians including pharmacology, allergy, dermatology, infectious diseases, nephrology and hepatology;
 - b. Nurses trained in performing and reading patch tests;
 - c. Administration staff for clinic booking and paperwork.
2. Laboratory
 - a. Technician (part-time) to process and store patient samples;
 - b. Consumables for clinic and laboratory work.

dermatologists, pharmacologists, infectious diseases, hepatologists and nephrologists. Specialist nurses trained in patch testing are already employed but the capacity in this area will be expanded. Both an in-patient referral service as well as an out-patient clinic will be used. The first successful clinic took place on the 11th September 2015. Fortnightly clinics will be started and frequency will be increased as the demand grows. Challenging cases from across the country will be discussed and readers are encouraged to email the authors for further discussions or if they are interested in being a part of this initiative to start a similar clinic in their own centres. The clinic will review any cases where a clinician is concerned about the possibility of an immune-mediated drug hypersensitivity reaction. The clinic will then manage and follow-up patients that fulfil current definitions for these reactions.

In order for a clinic of this nature to deliver an international standard of care, it will have certain basic requirements. Table I outlines these basic requirements under the headings of infrastructure, human resources and consumables. An important aspect for the clinic will be to develop the capacity to provide specialised *in vivo* testing for uncommonly used drugs or immunogenic excipients. For example, skin and intradermal testing protocols to test DHR to biologic therapies such as the TNF α blockers, e.g. infliximab, or access to photo patch testing equipment like Dermalight 80 MED and phototherapy units to elucidate photoallergic reactions to excipients such as titanium dioxide. Furthermore, to be fully actualised, the clinic will need to expand its research capacity by:

- i. Developing a functional, simple and secure database to store patient information;
- ii. Having the ethics and laboratory capacity in place to analyse data, collect and store relevant biological samples including tissue biopsies, peripheral blood

mononuclear cells and DNA/RNA; and

- iii. Establishing links with local and international collaborators that can help address complex basic science questions and train scientists in the many techniques needed to tackle the science of DHR.

These initiatives will require funding support and the clinic will need to think of innovative methods to acquire the necessary support in the current highly competitive funding environment.

ADVANTAGES OF THE MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC

From the above background and needs of a multidisciplinary drug hypersensitivity clinic, some of the key advantages are already evident. In Table II a summary of these and other additional advantages are listed. A multidisciplinary clinic of this nature is well aligned with the three core pillars of academic medicine:

- i. Clinical service;
- ii. Teaching; and
- iii. Research.

It will be a leading example of inter-disciplinary service and collaboration. If adequately supported, the clinic will provide a platform for care to be delivered at an international standard, focused on locally relevant DHRs. Training for specialists from all the disciplines involved as well as the upskilling of specialist nursing staff will be easy to co-ordinate. It is also hoped that high quality, management-altering research outputs will soon follow as the clinic grows and fosters local and international collaborations.

A multi-disciplinary clinic of this nature will also offer a centralised unit to co-ordinate and fulfil important surveillance and advocacy roles around DHRs. For instance, at present no prevalence data on DHRs from South Africa is available

TABLE II: ADVANTAGES OF THE MULTIDISCIPLINARY DRUG HYPERSENSITIVITY CLINIC

1. IMPROVED CLINICAL CARE AND PATIENT SATISFACTION:
 - a. In-patient referral service to aid clinicians with diagnostic and management challenges;
 - b. Capacity for cutting-edge evaluation of DHRs;
 - c. Single clinic visit for management of patients with multiple clinical problems;
 - d. Depth of experience built through centralisation of patients with uncommon DHRs.
2. CROSS-CUTTING SURVEILLANCE OF DHR SPECTRUM:
 - a. Determining local prevalences and allowing the opportunity to identify new emerging reactions.
3. HUMAN RESOURCE CAPACITY BUILDING AND TRAINING:
 - a. Training of specialists in managing DHR;
 - b. Training of specialised nurses;
 - c. Acquisition and training on state-of-the-art diagnostics (*in vivo* or *in vitro*);
 - d. Development of translational laboratory tools.
4. RESEARCH PLATFORM DEVELOPMENT TO ELUCIDATING MECHANISMS AND IDENTIFY USEFUL PREDICTIVE BIOMARKERS:
 - a. Hypothesis generation afforded from the opportunity to see the whole spectrum of a single drugs' hypersensitivity reactions;
 - b. Systematic data-recording, patient follow-up and link to laboratory to allow optimal translational research platform;
 - c. Pooled resources to improve success in accessing funding.
5. ADVOCACY, BOTH IN ACADEMIC AND PUBLIC SPHERES, TO RAISE AWARENESS TO THE BURDEN, MORBIDITY AND MORTALITY ASSOCIATED WITH SEVERE DHRS.

TABLE III: BRINGING IT ALL TOGETHER - THE RIFAMPICIN CASE STUDY**T-CELL MEDIATED DRUG HYPERSENSITIVITY REACTIONS:**

1. Severe cutaneous adverse reactions (SCAR).
 - b. Fixed drug eruptions;
 - c. Lichenoid drug eruptions;
 - d. DRESS;
 - e. SJS/TEN;
 - f. Acute generalised pustulosis.
2. Drug induced liver injury (DILI).
3. Tubular interstitial nephritis (TIN).

MULTIDISCIPLINARY CLINICAL APPROACH:

1. Joint patient review and clinical assessment to allow for the best possible clinical characterisation, with detailed clinical data collection.
2. Where clinically appropriate, ensuring pathological characterisation and tissue immunophenotyping through histology, blood compartment immunophenotyping and the storage of DNA and RNA.
3. Long-term follow-up data.

SAMPLE RESEARCH QUESTIONS THIS PLATFORM ALLOWS US TO TACKLE:

1. Are there any common predisposing factors or clinical characteristics to the above endotypes of rifampicin type IV hypersensitivity?
2. What are the immunological commonalities and differences that underlying the organ-specificity of rifampicin type IV hypersensitivity reactions?
3. Are there any predictive clinical or biomarkers when compared to control populations of HIV-infected and uninfected rifampicin exposed but non reacting patients?
4. What is the clinical and immunological cross-reactivity amongst the rifamycins?

for a number of commonly prescribed drugs including penicillins, rifampicin, or neuromuscular blockers. The lack of this information is a public health concern. In the USA, recent studies have begun to illustrate the consequences of incorrect penicillin allergy 'labelling'. Only about 1 in 20 patients self-reporting to doctors that they are penicillin allergic will have true hypersensitivity. The impacts of this has been shown to include increased antibiotic-related side-effects due to the use of alternatives, increased healthcare cost and length of hospitalisation.⁹ It is unknown if there is a similar problem and public health impact in South African hospitals. Similarly, the anaesthetists are struggling with a lack of information about which agents are preferable for South African populations, e.g. which neuromuscular blocker. Is it similar to international data or population specific? Consequently, proposals are already been worked on, together with anaesthetic collaborators and the UCT medicines information centre, to develop a centralised service to link patients experiencing peri- or intra-operative anaphylaxis with allergy testing. A database where anaesthetists could potentially look-up previous DHRs will be developed where future anaesthesia is required. This may in time become a valuable, life-saving resource. Undoubtedly, the clinic will provide a focal point for these and other types of surveillance and advocacy activities.

RIFAMPICIN DRUG HYPERSENSITIVITIES: A STARTING POINT FOR THE CLINIC

South Africa has one of the highest rates of active TB in the world and over 60% of all incident TB cases are HIV co-infected.¹⁰ Thus, TB drug induced hypersensitivity reactions are more common by virtue of increased exposure and hypersensitivity reactions are varied. For instance, rifampicin can cause the full spectrum of immune-mediated DHRs (Figure 1). However, the T-cell mediated type IV reactions are the commonest and usually

most serious (Table III).⁶ Consequently, the burden and complexity of these rifampicin T-cell mediated reactions are an excellent research area for the new clinic to focus on. In a recent pilot study, it was shown that in DRESS there is no cross-reaction with rifabutin, another equally effective rifamycin. If proven in larger studies, this has major implications in the retention of the more effective first-line regimen for treating TB.¹¹ In Table III a few of the key broad research questions have briefly been outlined and how the multidisciplinary clinic will address these questions. In addition, the clinic has an already expanding local and international collaborator base to develop the laboratory capacity. It is hoped that these collaborative efforts will be successful and either improve the management or predict the occurrence of these reactions.

CONCLUSION

It is exciting to embark on this new initiative of a multi-disciplinary drug hypersensitivity clinic. It is felt that it is long overdue given the ongoing burden of drug hypersensitivity reactions, their varied presentation and complex specific investigation and management requirements. It is hoped that this new platform will allow better management of the needs of the local population and also break new territory in the understanding and preventing of the often disastrous consequences of the medicines that are prescribed.

Other centres in South Africa are encouraged to start similar clinics and a network be developed so that work can be harmonised nationally.

REFERENCES

1. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, et al. The burden of non-communicable diseases in South Africa. *Lancet* (London, England) 2009;374(9693):934-47.
2. Mirakian R, Leech SC, Krishna MT, Richter AG, et al. Management of allergy to penicillins and other beta-lactams. *Clinical and Experimental Allergy: Journal of the BSACI* 2015;45(2):300-27.

3. Peter JG, Mouton JP, Lehloeny R. Immune-mediated hypersensitivity reactions in South Africa. *Curr Allergy Clin Immunol J* 2015;28(3):186-90.
4. De Prost N, Ingen-Housz-Oro S, Duong T, Valeyrie-Allanore L, et al. Bacteremia in Stevens-Johnson syndrome and toxic epidermal necrolysis: epidemiology, risk factors, and predictive value of skin cultures. *Medicine (Baltimore)* 2010;89(1):28-36.
5. Lehloeny R, Kgokolo M. Clinical presentations of severe cutaneous drug reactions in HIV-infected Africans. *Dermatol Clin* 2014;32(2):227-35.
6. Kannenberg SM, Jordaan HF, Koegelenberg CF, Von Groote-Bidlingmaier F, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome in South Africa: a 3-year prospective study. *QJM* 2012;105(9):839-46.
7. Knight L, Muloiwa R, Dlamini S, Lehloeny R. Factors associated with increased mortality in a predominantly HIV-infected population with Stevens Johnson syndrome and toxic epidermal necrolysis. *PLoS One* 2014;9(4):e93543.
8. Lehloeny R, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. *Int J Tuberc Lung Dis* 2011;15(12):1649-57.
9. Bourke J, Pavlos R, James I, Phillips E. Improving the Effectiveness of Penicillin Allergy De-labeling. *JACI-In practice*. 2015.
10. WHO. WHO Report 2014: Global tuberculosis control. Geneva: World Health Organisation, 2014 ISBN 978 92 4 156480 9.
11. Lehloeny R, Dlamini Muloiwa R, Kakande B, et al. Therapeutic trial of rifabutin following rifampicin-associated DRESS syndrome in TB-HIV co-infected patients. Submitted for Publication. 2015.

News

THE CERTIFICATE IN PAEDIATRIC ALLERGOLOGY – AN AUSPICIOUS FIRST!

RJ Green | S Kling | M Levin | E Weinberg

21 October 2015 will go down in the history of medicine in South Africa as an auspicious day. On this day, the first sub-specialist in Allergology passed her examination in the Certificate in Paediatric Allergology. Dr Talita Ferreira-Van der Watt is the first Paediatric Allergologist to achieve this status through examination in South Africa.

The sub-speciality in Allergology has come a long way. Allergology as a Division of Paediatrics started in Cape Town, at the Red Cross Children's Hospital, in the early seventies with Prof Eugene Weinberg joining the department. Prof Paul Potter was the first Fellow to train in Allergology in the early eighties. However, the idea of a formal sub-speciality in Allergology, started in the late nineties when Professors Weinberg and Potter lobbied the College of Medicine and HPCSA to register such a programme and examination. Then, over the last 15 years the work persisted with efforts by Professors Matt Haus, Sharon Kling, Mike Levin and Robin Green to make Allergology, as a recognised sub-speciality, a reality. A few years ago the HPCSA recognised Allergology as a sub-speciality of Paediatrics, Internal Medicine and Family Medicine. Since then just a handful of doctors have been credited as 'Grandfathers' in Allergology. However, much work has continued to formulate Rules and Regulations for examinations and setting up training facilities. Prof Mike Levin has led the charge to get Fellows trained and now Talita has achieved this landmark status.

The examination was in two parts – a written exam of two 3 hour papers in August 2015 and the oral/OSCE exam in October. The panel of examiners for this first exam were:

- Convenor and Examiner: Prof Robin Green



The examiners and candidate after the first successful Certificate in Paediatric Allergology

- Examiners: Prof Sharon Kling and Prof Mike Levin
- Moderator: Prof Eugene Weinberg

It was especially auspicious that Prof Weinberg was part of this first exam. He has brought Allergology to its natural crescendo. From today onward, we trust Allergology will take its place in the forefront of medicine and health, providing a service to needy South Africans with allergic illnesses.

Talita and Mike have set a very high standard in the training and examination of Allergologists. Now we move forward with the crusade to have Departments of Health, around South Africa, provide training posts and services in Allergology.