australasian society of clinical immunology and allergy

30 May 2019

Mr John Paul
Secretary, Pharmaceutical Benefits Advisory Committee (PBAC)
Department of Health and Ageing
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Dear Mr Paul,

Re: Dupilumab for atopic dermatitis

On behalf of the President and members of the Australasian Society of Clinical Immunology and Allergy (ASCIA) I am responding to your letter of 16 May 2019, regarding the use of dupilumab (Dupixent®) in moderate to severe atopic dermatitis (AD), commonly known as eczema.

I wish to advise that ASCIA strongly supports the application from Sanofi-Aventis Australia Pty Ltd to the PBAC for Pharmaceutical Benefits Scheme (PBS) listing of dupilumab, for the treatment of chronic, moderate to severe AD in adult patients who have had an inadequate response to topical therapies.

I am a consultant physician, clinical immunology and allergy, with over 40 years of experience in the field. I am Head of Department at Campbelltown Hospital and Professor, Clinical Immunology and Allergy, Western Sydney University (WSU). I am convenor of the Graduate course and Masters in Medicine (Allergic diseases) at WSU. I am a past president of ASCIA and the current Chair of the ASCIA working parties for Hereditary Angioedema (HAE) and Chronic Spontaneous Urticaria (CSU). I have had a particular clinical and research interest in allergic skin diseases and I continue to participate in specialised clinics for patients with AD.

The following information is submitted in response to your specific enquiries, for consideration at the June ESC meeting and the July 2019 PBAC meeting.

ASCIA is strongly supportive of the proposal that patients with chronic, moderate to severe AD be eligible for treatment with dupilumab. At the present time, if patients fail to achieve a good response to topical management when compliance and adherence are adequate, the only option is to consider various immunosuppressive treatments, all of which have weak evidence base, considerable possible side effects, long term effects and need for frequent monitoring including blood tests. An alternative to this situation is needed.

Assessment of severity and response to treatment
As your question outlines, there are a number of severity assessment tools in use for AD.

PGA
The physician global assessment (PGA) score (termed the investigator global assessment score-IGA-when used in clinical trials), is an easy and rapid tool for assessing disease severity. It has been used

as an assessment of severity and as an outcome tool in approximately a third of all clinical AD trials, especially those organised in the USA. While its ease of use is an advantage, it has not been standardised, and there are various scales (e.g. 0-4 or 0-5) in use, as well as variable definitions for each point on the scale. It lacks consideration of body surface area involved, is not weighted for high impact areas (such as involvement of the hands or face) and has no patient related component or symptom burden aspect.

Despite these short comings, providing the scale is defined and clearly described, it will aid in defining severity for moderate to severe disease (3 or 4 on a 0-4 scale). A change in PGA from 3-4 to 0-2 signifies a positive response to an intervention *(Futamura M et al. J Am Acad Dermatol 2016;74:288-94).*

EASI

The eczema area and severity index (EASI) score is a validated score that measures severity and extent of key features of AD. It has been used extensively as a tool for qualifying patients for entry into therapeutic trials, as well as a primary or secondary endpoint for measuring efficacy of treatments.

It has a number of disadvantages:

- It is complex to use and has not been employed in routine clinical practice until very recently, by the majority of physicians.
- It requires some training to become competent in its application.
- It lacks weighting for high impact areas (such as involvement of the hands or face).
- It has no patient assessment domain.

For these reasons ASCIA members do not favour the use of EASI as the severity assessment tool or as a means of assessing treatment efficacy.

DLQI

The dermatology life quality index (DLQI) was developed in 1994 to measure dermatological patients' quality of life (QoL) and it is the most commonly used measure in clinical trials. To be clinically useful, QoL measurement instruments must have demonstrated psychometric properties such as validity, reliability and responsiveness to change.

The DLQI has been shown to be a reliable and valid instrument (*Basra MKA, Fenech R, Gatt RM, et al: The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. Br J Dermatol 2008; 159: 997–1035.)*

Crucially, responsiveness to change is important for instruments designed to measure change over time. The responsiveness of an instrument to change is directly related to the magnitude of the change in a patient's QoL score. However, the statistical significance of a change in score does not necessarily imply that the score change is also clinically important.

The minimal clinically important difference (MCID) has been defined as 'the smallest difference in score in the domain of interest which patients perceive as beneficial'. For the physician, meaningful change may be one that indicates the value of a treatment or the need for a change in treatment. Recently this has been examined and validated for the DLQI with a change of 4 in the score being deemed the MCID *(Basra MKA et al. Dermatology 2015; 230:27–33).*

Advantages of DLQI as a tool for assessing severity and responsiveness to treatment:

- It is used widely in clinical practice.

- It is a patient self-assessment.
- It is simple and quick to use, taking 2-3 minutes to complete.
- It is able to reflect disease impact in those patients with AD involvement of high impact areas such as the hands and face, where this is not acknowledged in EASI.
- It has a defined and validated MCID of 4.

ASCIA members favour the combined use of **PGA** (with a specified description of the various attributes within the scale) and **DLQI** for both assessment of severity for eligibility for treatment with dupilumab and for assessment of response to treatment.

Suitability of Clinical Immunology/Allergy Specialists to prescribe dupilumab

Clinical immunology/allergy specialists undergo broad and in depth training in all aspects of allergic diseases. The Royal Australasian College of Physicians (RACP) Clinical Immunology and Allergy Advanced Training Curriculum outlines, in detail, the expected core competencies for those training in this discipline. This includes a detailed knowledge of the basic and clinical science underpinning allergic skin disorders including AD. Therefore, qualified clinical immunology/allergy specialists are well placed to meet the needs of those presenting with AD, indeed this group of patients constitute a significant proportion of our referral patient population. Many colleagues are involved in severe eczema clinics either as a stand-alone service or as part of a multi-disciplinary team with specialised nursing staff, dietitians and dermatologists.

In addition, clinical immunology/allergy specialists are qualified and experienced in prescription and administration of the newer biologic agents for a number of immune-mediated and allergic disorders and understand appropriate selection and monitoring of these patient groups.

We hope that this letter provides sufficient information for the proposed PBS listing of dupilumab to be considered at the June ESC meeting and at the July 2019 PBAC meeting.

Yours sincerely,

Prof Connie Katelaris MBBS PhD FRACP
Chair, ASCIA HAE and CSU Working Parties
Past ASCIA President

Copy:
Dr Brynn Wainstein MBChB PhD FRACP
ASCIA President

Declaration of potential conflicts of interest of author:
I am a principal investigator for clinical trials using dupilumab in severe asthma. I have not received personal payments for this work. I have received honoraria for presentations on management of severe asthma at conferences and for participation in a Sanofi advisory board.