Received: 7 March 2024 | Accepted: 29 May 2024

DOI: 10.1111/ajd.14333

BRIEF REPORT

Australasian Journal of Dermatology

Barriers to the introduction of novel advanced targeted treatments for Australian dermatology patients: Are skin diseases symptomatic of a systemic healthcare problem?

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Abstract

The aim of this article is to provide education to clinicians about certain barriers restricting the use of advanced targeted treatments in Australian health care. For illustrative purposes, the article focuses on dermatological conditions, but the content is relevant to all specialties that treat inflammatory and chronic diseases. Barriers to care discussed result in a lower than necessary standard of care for patients in Australia despite important advancements in medicine.

KEYWORDS

atopic dermatitis, equity, health economics, paediatric dermatology, psoriasis

INTRODUCTION

Autoimmune and inflammatory skin diseases have substantial impacts on patients' mental, social, physical and environmental quality of life, leading to internal and external stigma, avoidance behaviours and barriers to education, career and relationships, including with family and children.[1] Until relatively recently, available treatments have largely been non-targeted, variably effective and usually immunosuppressive in nature.[2] These agents are typically associated with significant long- and short-term toxicities and other safety concerns. Unfortunately, for many patients, they remain the (frequently off-label) standard of care.[2]

More recently, the uptake of advanced targeted treatments (ATTs) for psoriasis and other common inflammatory conditions has revolutionised treatment outcomes for patients with these severely debilitating

diseases. In general, ATTs have a far more robust safety and efficacy profile compared to broad-spectrum immunosuppressants. Yet, patients face multiple barriers to access novel ATTs through Australia's Pharmaceutical Benefits Scheme (PBS), particularly in the context of skin diseases and other chronic conditions, including a lack of commercial incentives for manufacturers, the application of narrow health economic criteria by public decision-makers and strict patient eligibility requirements.

COMMERCIAL DISINCENTIVES

While there is a limited range of novel ATTs for well-represented conditions, such as psoriasis, specific contraindications and intolerances necessitate a more diverse range of therapeutic options. So-called 'personalised targeted treatment' has the potential to allow prescribing tailored to patients' individual clinical circumstances. Unfortunately, in patient populations where a number of therapeutic agents already exist, for example, psoriasis, ATTs face a number of commercial barriers to market entry. Notwithstanding the clinical superiority of emerging ATTs, it may not be financially attractive for pharmaceutical sponsors to seek entry within an already saturated market segment. For example, two highly efficacious, US Food and Drug Administration approved biological agents for the treatment of psoriasis (brodalumab and mirikizumab) have not been submitted for consideration by the Pharmaceutical Benefits Advisory Committee (PBAC) for this indication.

The Federal Government's reliance upon risk-sharing agreements (RSAs) comprises another commercial obstacle to the introduction of ATTs in Australia. RSAs are commonly used by the Department of Health and Aged Care to manage various forms of clinical and financial uncertainty—including the extent of a new drug's anticipated health benefits, cost-effectiveness, usage and budgetary impact—and typically include provisions to shift perceived financial risk onto sponsors through rebate arrangements.[3] With respect to severe atopic dermatitis, for example, current RSA provisions shift the cost burden of treating patients beyond a set number back onto pharmaceutical sponsors, effectively disincentivising the introduction of new ATTs for this condition in Australia.

Given the litany of costs faced by sponsors in the launch of a new drug—including, among others, research and development, clinical trials, health economic analyses, pharmacist and clinician input, and regulatory, legal and marketing expenses as well as significant submission fees to the PBAC[4]—the financial case becomes increasingly fraught for all but the highest performing 'blockbuster' drugs. Pemphigus vulgaris, for example, is a rare autoimmune blistering disease associated with significant morbidity and mortality. The condition has no approved therapeutic agent in Australia and off-label use of broad-spectrum immunosuppressants is often ineffective, with significant risk due to the doses required. Rituximab is highly efficacious for pemphigus vulgaris and recent S2k guidelines have listed it as a first-line therapy for all degrees of severity.[5] However, with relatively low disease prevalence and rituximab now 'off-patent', sponsors have little incentive to undertake a submission to the PBAC for this indication.

HEALTH ECONOMIC CRITERIA

The Pharmaceutical Benefits Advisory Committee's requirements to demonstrate cost-effectiveness exacerbate the financial calculus faced by sponsors. As treatment options become increasingly 'personalised', small patient populations within ever more specific indications make it increasingly difficult to demonstrate cost-effectiveness through traditional approaches to clinical trials. As the PBAC is likely to interpret greater uncertainty in efficacy data as risk to be borne by the sponsor, there is dwindling corporate appetite to investigate ATTs for rare conditions, let alone to attempt to bring them to market. For example, hidradenitis suppurativa and pyoderma gangrenosum are significant inflammatory dermatological conditions with well-described morbidity that have been shown to respond to a number of biological agents currently used for the treatment of psoriasis.[6,7] Despite this, since December 2016, only two ATTs have been approved by the Therapeutic Goods Administration (TGA) for treatment of hidradenitis suppurativa (adalimumab, secukinumab) of which only one is reimbursed by the PBS and none for pyoderma gangrenosum.

In populations suffering chronic disease, it is often difficult to demonstrate the relative cost-effectiveness of a new high-cost therapy, particularly where a condition is highly prevalent and has had decades of low-cost (if inadequate) treatment options. Atopic dermatitis is one such condition—with high prevalence and entrenched morbidity, the negative consequences of this illness may be of such magnitude that they cannot be adequately quantified in standard cost-effectiveness models. Studies have shown that atopic dermatitis, for example, bears substantial direct and indirect costs to patients and the community, including high out-of-pocket costs, reduced educational attainment, increased absenteeism and presenteeism and a range of associated opportunity costs to the broader economy.[8]

In conditions with large unmet therapeutic needs, in which the accepted underlying mechanisms of diseases are many and complex, the demand for personalised targeted treatment is even greater. However, where there is high unmet need and prevalence, the total cost of subsidising ATTs would be commensurately high. Perceived financial risk (i.e. total budgetary impact) has generally led the PBAC to reserve the use of ATTs for only the most severe cases. As a result, patients with common conditions such as moderate atopic dermatitis are unable to access ATTs, perversely, because the burden to patients and the community is so great. Where ATTs offer enhanced quality of life, efficacy, tolerability and safety compared to other traditional immunosuppressive agents, then logically this may translate into factors such as reduced stigmatisation, increased employment and relationship opportunities, among others.

PATIENT ELIGIBILITY

Once ATTs are made available via the PBS, patients face further barriers to access. Even for patients with severe disease, access to an ATT frequently requires patients to endure months-long prior exposure to potentially toxic, less effective agents. Notwithstanding often severe toxicities, patients who respond to such agents may fail to meet mandated 'severity' criteria, rendering them ineligible to access clinically superior alternatives. For example, if a patient on treatment for psoriasis is on an immunosuppressive agent such as cyclosporin, and as such has a baseline Psoriasis Area and Severity Index (PASI) score of >15 (PASI being the main form of assessment of psoriasis in Australia) and is responding so as their PASI score is <15, then they will not be eligible for safer and more effective ATTs despite the inherent long-term risks.

Restrictive patient eligibility criteria are also evident with respect to access to ATTs for paediatric patients. Children with psoriasis, for example, may endure significant physical and psychological morbidity during key periods of development, with decades-long subsequent impacts.[9] Yet, these patients may be denied therapeutic options not due to demonstrated issues about safety, quality or efficacy, but because of their age, the division of adult and paediatric populations is largely down to clinical trial design and a range of well-documented ethical and practical barriers to the recruitment of children.[10] The resulting lack of evidence among younger patients leads to apprehension from both regulatory and reimbursement perspectives, resulting in systemic inequity of access. For example, 11 agents have been indicated by the TGA for adult patients with psoriasis, as opposed to only four in paediatric and adolescent patients.

CONCLUSION

For hundreds, if not thousands of years, cutaneous symptoms have been recognised as the first manifestation of systemic disease. Ironically, barriers to the effective treatment of skin disease may likewise be a bellwether of systemic faults in Australia's own healthcare system. Considering the rapid evolution of ATTs and emergent possibilities for 'personalised medicine', Australia's medication reimbursement system appears increasingly unfit for purpose. There is a shared interest—and opportunity—between the government, industry, clinicians and patients to provide the right drug to the right patient, to achieve the best possible outcomes, at the lowest cost and with the least potential harm. Yet, Australian patients continue to face a range of barriers to access ATTs for the treatment of inflammatory dermatological conditions, including uncertain and inappropriate clinical trial data, low commercial appeal and health economic and budgetary hurdles. The net result is a lower than necessary standard of care for patients in Australia despite important advancements in medicine.

A shift in perspective by regulatory bodies is perhaps necessary to consider a broader range of positive outcomes, including enhanced productivity, in the evaluation of cost-effectiveness of drugs for common, burdensome conditions. The design of clinical trials must do the same. This may allow for a more inclusive reimbursement process for novel agents in conditions with high unmet needs and, in the process, allow for the alleviation of enormous suffering and collective loss to society.

ACKNOWLEDGEMENTS

None. Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

The following authors have been investigators, speakers, advisors, consultants, employees and/or have received travel grants from the following companies. PDM: Novartis, AstraZeneca, Abbvie, Pfizer, Bristol-Meyers Squibb, Eli Lilly and Company and Boehringer Ingelheim. Associate Professor Mahar is a former employee of and owns equity in, Eli Lilly & Company. Associate Professor Mahar is an editorial board member of the *Australasian Journal of Dermatology* and a co-author of this article. To minimise bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. AC: Miss Crothers is a former PBAC and MSAC evaluator. PF: AbbVie, Akaal, Amgen, Apogee, Arcutis, Argenx, Aslan, AstraZeneca, BMS, Boehringer Ingelheim, Botanix, Celgene, Celtaxsys, CSL, Cutanea,

Dermira, EVELO Biosciences, Galderma, Genentech, GenesisCare, GSK, Hexima, Incyte, Janssen, Kymab, Leo Pharma, Eli Lilly and Company, Mayne Pharma, MedImmune, Melaseq/Geneseq, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals Inc, Reistone, Roche, Sanofi, Sun Pharma, Takeda, Teva, UCB Pharma, Valeant and Wintermute. JT: None declared.

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How to cite this article: Mahar PD, Crothers A, Foley P, Thomas J. Barriers to the introduction of novel advanced targeted treatments for Australian dermatology patients: Are skin diseases symptomatic of a systemic healthcare problem? Australas J Dermatol. 2024;65:e164–e167. https://doi.org/10.1111/ajd.14333