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**Manuscript Title:** Combination treatment with monoclonal antibodies: secukinumab, benralizumab and dupilumab for the combined management of psoriasis and severe asthma

**Running Title:** Combined treatment with multiple biologics

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**Disclosures:**
None of the above disclosures were involved at any point in the enclosed manuscript.

**Acknowledgements:**
None

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/AJD.13676

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Combination treatment with monoclonal antibodies: secukinumab, benralizumab and dupilumab for the combined management of psoriasis and severe asthma

Abstract

Biological disease modifying agents have increasingly become available for the effective treatment of both cutaneous and non-cutaneous inflammatory conditions. We report a case of a woman treated successfully for psoriasis and psoriatic arthritis with the IL-17 inhibitor secukinumab whilst simultaneously being treated for severe asthma and nasal polyps, initially with the IL-5 inhibitor benralizumab, followed by dupilumab, a monoclonal antibody that targets the IL-4 receptor alpha subunit which blocks signalling from both IL-4 and IL-13.

Introduction

Biological disease modifying agents have increasingly become available for the effective treatment of both cutaneous and non-cutaneous inflammatory conditions.\textsuperscript{1,2,3}

Despite the increasing use of biological agents across different indications, there is a paucity of data around the simultaneous use of more than one biological agent. What little data exist usually centre around the combined biological treatment of one specific indication. Reported examples include the treatment of asthma with combined omalizumab and mepolizumab, as well as rheumatoid arthritis with various combinations of TNF-alpha inhibitors, anakinra, abatacept and rituximab.\textsuperscript{4,5,6,7,8} A number of reports have also described treatment of inflammatory bowel disease with multiple biological agents, usually a TNF-alpha agent combined with either ustekinumab or vedolizumab.\textsuperscript{9} From a
dermatological perspective, the use of combined dupilumab and guselkumab has been reported to treat psoriasis with either comorbid atopic dermatitis or bullous pemphigoid.\textsuperscript{10}

We report a case of a woman treated successfully for psoriasis and psoriatic arthritis with the IL-17 inhibitor secukinumab whilst simultaneously being treated for severe asthma and nasal polyps, initially with the IL-5 inhibitor benralizumab, followed by dupilumab, a monoclonal antibody that targets the IL-4 receptor alpha subunit which blocks signalling from both IL-4 and IL-13.

**History**

In August 2018, a 40 year old woman was recruited into the OASIS-2 trial ‘A multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of mirikizumab to secukinumab and placebo in patients with moderate-to-severe plaque psoriasis’ for the management of her severe chronic plaque psoriasis.

At baseline, she had a Psoriasis Area and Severity Index (PASI) of 15.2, a Nail Psoriasis Severity Index of 54/80 indicating significant fingernail dystrophy, genital involvement, a Dermatology Life Quality Index (DLQI) score of 27/30 and an Early ARthritis for Psoriatic patients questionnaire (EARP) score of 5.

In addition to chronic plaque psoriasis with psoriatic arthritis, the patient had several comorbidities, including a history of depression, dyslipidaemia and aspirin exacerbated respiratory disease (AERD) with onset in 2008: the last of these comorbidities characterised by increasingly severe adult-onset non-atopic eosinophilic asthma, chronic rhinosinusitis with nasal polyposis and non steroidal anti-inflammatory drug (NSAID) hypersensitivity.

Following recruitment into the clinical trial, her psoriasis responded exceedingly well, resulting in complete clearance of her cutaneous symptoms with a PASI 0 and DLQI 0/30 in August 2019, along with a substantial subjective improvement in symptoms of psoriatic arthritis.
Unfortunately, her asthma control substantially worsened over her time in the trial, with an increase in her asthma symptoms including night waking and a deterioration in spirometry with emergence of significant bronchodilator reversibility, despite escalation of asthma therapy including high dose inhaled corticosteroids, long-acting beta-agonist (ICS/LABA) and oral prednisolone. The asthma had been gradually worsening over the preceding several years and it was not considered likely that the study medication was causal. Her withdrawal from the OASIS-2 study in September 2019, after 12 months in the trial, was necessitated by a switch to the add-on biologic therapy of benralizumab, commenced in August 2019 for uncontrolled asthma. She had a degree of improvement of her asthma with this therapy; her Asthma Control Questionnaire-5 (ACQ5) score (a validated symptom scale assessing degree of asthma control) fell significantly from 4.0 to 2.0, although there was no tangible change in her spirometry at this time.

In March 2020, she was reviewed in a dermatological biologics subspecialty clinic as her joints and skin had subsequently flared from a psoriatic arthritis and psoriasis perspective, respectively. A precise PASI was not undertaken as the consultation was performed via telehealth in the context of COVID-19. In order to control her asthma and arthritis, she was taking 25 mg prednisolone daily as well as continuing twice daily inhaled therapy and subcutaneous benralizumab 30 mg every 8 weeks. Following consultation with her immunologist, an extensive discussion was had with the patient as to whether she should recommence a biological agent to manage her psoriasis and psoriatic arthritis.

With reference to her potential previous clinical trial exposure, secukinumab, an anti-interleukin 17 monoclonal antibody, was the agent chosen to consider commencing due to its efficacy in both chronic plaque psoriasis and psoriatic arthritis. Mirikizumab, an anti-interleukin 23 monoclonal antibody, was not approved by the Therapeutic Goods Administration for psoriasis or psoriatic arthritis at the time.

It was explained to the patient that there were no published data supporting the efficacy of combining benralizumab and secukinumab (the latter of which was obtained on compassionate grounds as the patient did not meet the Pharmaceutical Benefits Scheme qualification criteria). It was further discussed with the patient that combining the agents...
would be met with a degree of unquantifiable risk in the absence of data supporting their safety and efficacy together. During this consultation in March 2020, the patient stated that the impact of her psoriasis and psoriatic arthritis on her quality of life was so substantial that she would rather cease benralizumab and recommence an agent indicated for psoriasis and psoriatic arthritis. This conversation was complicated by the then-emerging COVID-19 pandemic and additional uncertainty surrounding the impact COVID-19 might have upon patients on biological agents. However, there was a general clinical consensus among her treating clinicians that her risk, should she be exposed to COVID-19, of developing severe COVID-19 complications would be greater with uncontrolled asthma and chronic prednisolone use, as well as uncontrolled psoriasis and psoriatic arthritis, than the use of one or more monoclonal, non-immunosuppressive agents.

**Progress of psoriasis**

Following the induction period associated with the commencement of secukinumab in March 2020, she continued on 300 mg monthly. The patient substantially improved in terms of her chronic plaque psoriasis, psoriatic arthritis and nail psoriasis.

By June 2020, her psoriasis severity corresponded with a PASI score of 1.0 with noticeable improvement in nail psoriasis and symptoms of psoriatic arthritis.

One minor complication in her treatment involved a temporary dosing error, where the patient was administering secukinumab 300 mg every second month (the dosing interval of benralizumab). During this period of time, the patient observed a mild flare of psoriasis and arthralgia which was alleviated upon clarification of dosing schedules and recommencement of monthly secukinumab 300 mg.

**Progress of asthma**

While receiving secukinumab and benralizumab, the asthma remained incompletely controlled. When access to dupilumab became available, a switch was discussed as this agent has a differing mode of action (acting against IL-4 and IL-13, rather than IL-5), has

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data to support efficacy in nasal polyposis, which was of great symptomatic concern to the patient and was also considered to offer the possibility of further clinical improvement than what had been achieved to date. She commenced dupilumab (loading dose of 600 mg then 300 mg every 2-weeks subcutaneously) in November 2020; this has been well tolerated and associated with greater asthma control. The ACQ5 had fallen further to 0.8 (a score of 0.75 is classified as well-controlled asthma).

**Adverse events**

In terms of potential adverse events, mild liver function derangement was measured, dominantly elevation of gama-glutamyl transferase (GGT) with no synthetic dysfunction. This was likely multi-factorial hepatic steatosis attributable to weight gain from reduced exercise, protracted use of oral prednisolone and the patient’s increased alcohol consumption during the extended COVID-19 lockdown in Melbourne, Australia. The values improved upon follow-up liver function testing and so this is not considered to be attributable to either secukinumab or dupilumab.

The patient also suffered from occasional sweating episodes and rhinorrhoea, which were mild in nature and not associated with any other signs or symptoms. The patient has suffered no additional adverse effects as a result of the combination of secukinumab and dupilumab.

**Recent progress**

At the time of writing in June 2021, the patient is convinced that the benefit she derives from the combination of both dupilumab and secukinumab for her multiple co-morbidities substantially outweighs any theoretical risk of combination therapy.

Her most recent PASI score was 2.2. Her severe asthma is now well controlled, and her nasal polyposis which has had a substantial effect on her quality of life is not troubling her.
Importantly, her prednisolone has continued to be weaned and is currently at a daily dose of 4mg.

**Conclusion**

The advent of monoclonal antibody therapies has brought immense improvement to many severe and previously difficult-to-control diseases across a range of clinical specialties. However, there is uncertainty about the efficacy and safety of simultaneous use of these novel biological agents which target different cytokines.

The overall safety profile of these agents, with their very targeted mode of action, in contrast to traditional immunosuppressants, suggests a favourable risk/benefit profile when used in combination and may be an appropriate therapeutic strategy if introduced with appropriate informed consent. That said, the safety of combination immunomodulatory medications cannot be assumed, particularly with respect to infection and malignancy, and heightened surveillance of adverse effects and potential complications is prudent. Further, little is known about the potential drug-to-drug interactions when combining biologic agents. This may be of particular relevance in the context of dupilumab (and anti-IL13 agents in development) and psoriatic disease, a protective role for IL-4/IL-13 has been suggested in inflammatory diseases of the IL-23-IL-17 axis. Inclusion of cases such as this in the literature and in registries will help guide future management of patients with multiple inflammatory conditions.

The magnitude of effect of combined agents on quality of life with respect to multiple comorbidities is illustrated in this case report. Such treatment may provide substantial relief of suffering for specific patient populations. Continued scrutiny and discussion regarding such treatments in challenging clinical cases may well provide opportunities for future care.

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Title:
Combination treatment with monoclonal antibodies: Secukinumab, benralizumab and dupilumab for the combined management of psoriasis and severe asthma

Date:
2021-08-09

Citation:

Persistent Link:
http://hdl.handle.net/11343/298831