REMISSION OR SUPER RESPONDER

SPECIAL TWO PART SERIES

Remission or ‘super responders’ in severe asthma: what should we target and when should we switch?

MAT-AU-2302032 | Date of preparation August 2023| Sanofi Australia (Macquarie Park, NSW)

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

PANEL FOR TONIGHT'S MEETING

Prof Phil Bardin (Chair)
Respiratory
Professor of Respiratory Medicine in the Faculty of Medicine, Nursing & Health Sciences, and Director, Lung Sleep Allergy & Immunology, Monash University and Medical Centre, Melbourne

A/Prof Joy Lee
Respiratory/ Immunology
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Respiratory/ Immunology
Head of Allergy, Asthma & Clinical Immunology, the Alfred Hospital; Clinical Professor, School of Public Health & Preventive Medicine, Monash University

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

CHAIR

Prof Phil Barden

Professor of Respiratory Medicine in the Faculty of Medicine, Nursing & Health Sciences, Monash University, Melbourne

Phil is Recognised for investigation of obstructive lung diseases (particularly virus-asthma-COPD exacerbations) and has conducted research on new asthma and COPD therapies. Recently research has examined vocal cord dysfunction in obstructive lung diseases.

Professional activities reflect a career-long commitment to research and medical education, particularly in the areas of asthma and COPD. Recipient of ongoing Australian NH&MRC funding, chaired Australian NH&MRC Respiratory Grant Review Panel and served on the NH&MRC Academy. Currently Co-Editor of Respirology, official journal of the TSANZ and APSR.

ADVENT
TYPE 2 INFLAMMATORY DISEASES

REMISSION
OR
SUPER RESPONDER

SPECIAL TWO PART SERIES

Remission in rheumatology: concept of treat to target

Dr Michelle Tellus

Consultant Rheumatologist

Private Practice,

Melbourne

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

SPEAKER

Dr Michelle Tellus

Consultant Rheumatologist, Private Practice, Melbourne

Dr Michelle Tellus' interests lie within inflammatory diseases of the joints and muscles and in the field of osteoporosis. Dr Tellus has worked at the Royal Melbourne Hospital, Bone and Mineral Unit of the Royal Children's Hospital as a Research and in the field of Juvenile Chronic Arthritis and at the Essendon Hospital Bone and Metabolic Unit Outpatients Team.

Disclosures

No disclosures.

TREATMENT STRATEGIES AND RECOMMENDATIONS

Treat to target

Recommendations of an international task force

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

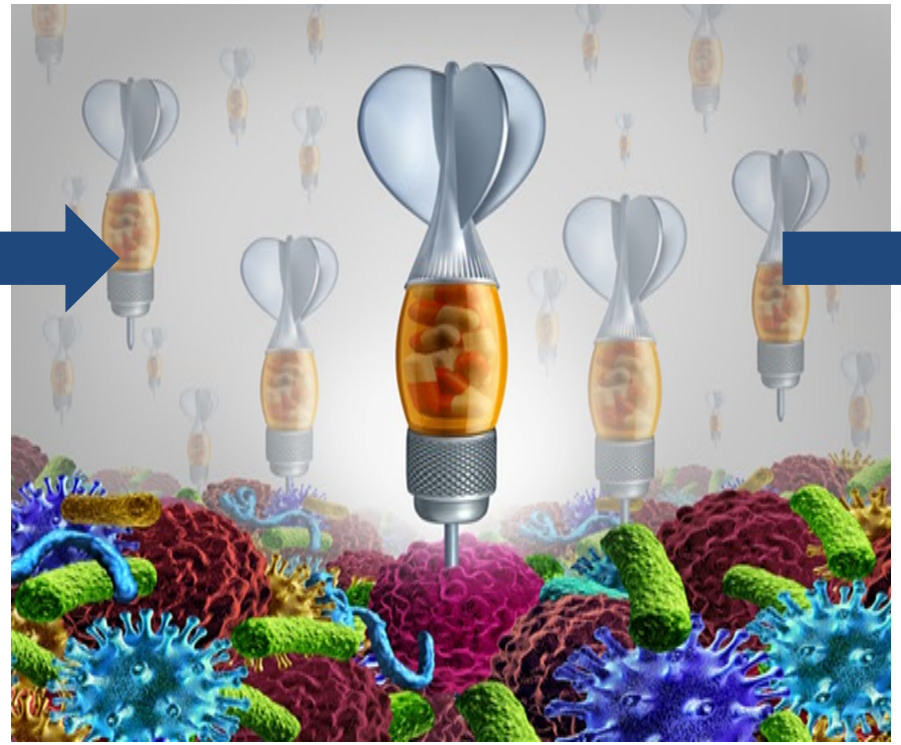
Treatment strategies and recommendations: overview

The treatment target is remission or a state of at least low disease activity, which should be attained within 6 months

First-line therapy

MTX should be prescribed at an optimal dose of 25 mg weekly and in combination with glucocorticoids

40–50% of patients reach remission or at least low disease activity with this regimen



Second-line therapy

If first-line treatment fails, sequential application of targeted therapies, such as bDMARDs or JAK inhibitors in combination with MTX, should be prescribed

>75% of these patients reach the treatment target over time

bDMARD, biological disease-modifying antirheumatic drug; **JAK**, Janus kinase; **MTX**, methotrexate

Aletaha D, et al. JAMA. 2018;320:1360–1372.

TREATMENT STRATEGIES AND RECOMMENDATIONS

EULAR recommendations for the management of RA

eular

2022 Update

EULAR, European Alliance of Associations for Rheumatology; **RA,** rheumatoid arthritis

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

EULAR recommendations: overarching principles


EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 up

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ABSTRACT

Objectives To provide an update of the EULAR rheumatoid arthritis (RA) management recommendations addressing the most recent developments in the field.

Methods An international task force was formed and solicited three systematic literature research activities on safety and efficacy of disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids (GCs). The new evidence was discussed in light of the last update from 2019. A predefined voting process was applied to each overarching principle and recommendation. Levels of evidence and strengths of recommendation were assigned to and participants finally voted on the level of agreement with each item.

Results The task force agreed on 5 overarching principles and 11 recommendations concerning use of conventional synthetic (cs) DMARDs (methotrexate (MTX), leflunomide, sulfasalazine), GCs; biological (b) DMARDs (tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab including biosimilars), abatacept, rituximab, tocilizumab, sarilumab and targeted synthetic (ts) DMARDs, namely the Janus kinase inhibitors tofacitinib, baricitinib, filgotinib, upadacitinib. Guidance on monotherapy, combination therapy, treatment strategies (treat-to-target) and tapering in sustained clinical remission is provided. Safety aspects, including risk of major cardiovascular events (MACEs) and malignancies, costs and sequencing of b/tsDMARDs were all considered. Initially, MTX plus GCs is recommended and on insufficient response to this therapy within 3–6 months, treatment should be based on stratification according to risk factors. With poor prognostic factors (presence of autoantibodies, high disease activity, early erosions

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Smolen JS, et al. Ann Rheum Dis 2022;0:1–16. doi:

A. Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist

B. Treatment decisions are based on disease activity, safety issues, and other patient factors, such as comorbidities and progression of structural damage

C. Rheumatologists are the specialists who should primarily care for patients with RA

D. Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life

E. RA incurs high individual, medical, and societal costs, all of which should be considered in its management by the treating rheumatologist

As in previous versions of these recommendations, the task force continued to use overarching principles for information on the general aspects of the management of RA.
EULAR, European Alliance of Associations for Rheumatology; **RA**, rheumatoid arthritis

EULAR recommendations: initial therapy

1. Therapy with DMARDs should be started as soon as the diagnosis of RA is made
2. Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient
3. Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted
4. MTX should be part of the first treatment strategy
5. In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy
6. Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible[a]

Recommendations 1–5 remain unchanged.

[a]Small change implemented: Recommendation 6 now explicitly and unequivocally advocates not only a rapid tapering regimen, but also timely discontinuation.

csDMARD, conventional synthetic disease-modifying antirheumatic drug; **DMARD**, disease-modifying antirheumatic drug**; EULAR**, European Alliance of Associations for Rheumatology; **MTX**, methotrexate; **RA**, rheumatoid arthritis

Smolen JS, et al. Ann Rheum Dis. 2023;82:3–18.

EULAR recommendations: treatment failures

7. If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered
8. If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK inhibitors may be considered, but pertinent risk factors[a] must be taken into account[b]
9. bDMARDs and tsDMARDs[a] should be combined with a csDMARD; in patients who cannot use csDMARDs as co-medication, IL-6 pathway inhibitors and tsDMARDs[a] may have some advantages compared with other bDMARDs
10. If a bDMARD or tsDMARD[a] has failed, treatment with another bDMARD or tsDMARD[a] should be considered; if one TNF or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF/IL-6R inhibitor[c]

[a]The following risk factors for CV events and malignancies must be considered when intending to prescribe a JAK inhibitor: Age over 65 years; history of current or past smoking; other CV risk factors (e.g. diabetes, obesity, hypertension); other risk factors for malignancy (current or previous history of malignancy other than successfully treated non-melanoma skin cancer); risk factors for thromboembolic events (history of myocardial infarction or heart failure, cancer, inherited blood clotting disorders, or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery, or immobile). Recommendations 7 and 9 remain unchanged. [b]Most extensive change implemented: Following new safety issues emanating from the ORAL-Surveillance trial, recommendation 8 now places JAK inhibitors at the same level as bDMARDs, but only in patients in whom risk factors for CV or malignant diseases have been considered specifically. [c]Small change implemented: IL-6R inhibition has now been tested after insufficient response to another IL-6R blocker, leading to the inclusion of IL-6R blockade in addition to TNF inhibition in patients in whom a previous bDMARD with the same mechanism of action has failed.

bDMARD, biological disease-modifying antirheumatic drug; **csDMARD**, conventional synthetic disease-modifying antirheumatic drug; **CV,** cardiovascular; **EULAR**, European Alliance of Associations for Rheumatology; **IL-6**, interleukin-6; **IL-6R**, interleukin-6 receptor; **JAK**, Janus kinase; **TNF**, tumour necrosis factor; **tsDMARD**, targeted synthetic disease-modifying antirheumatic drug

Smolen JS, et al. Ann Rheum Dis. 2023;82:3–18.

EULAR recommendations: remission

11. After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs[a] and/or csDMARDs) may be considered

Recommendations 11 and 12 from 2019 were brought together as recommendation 11.

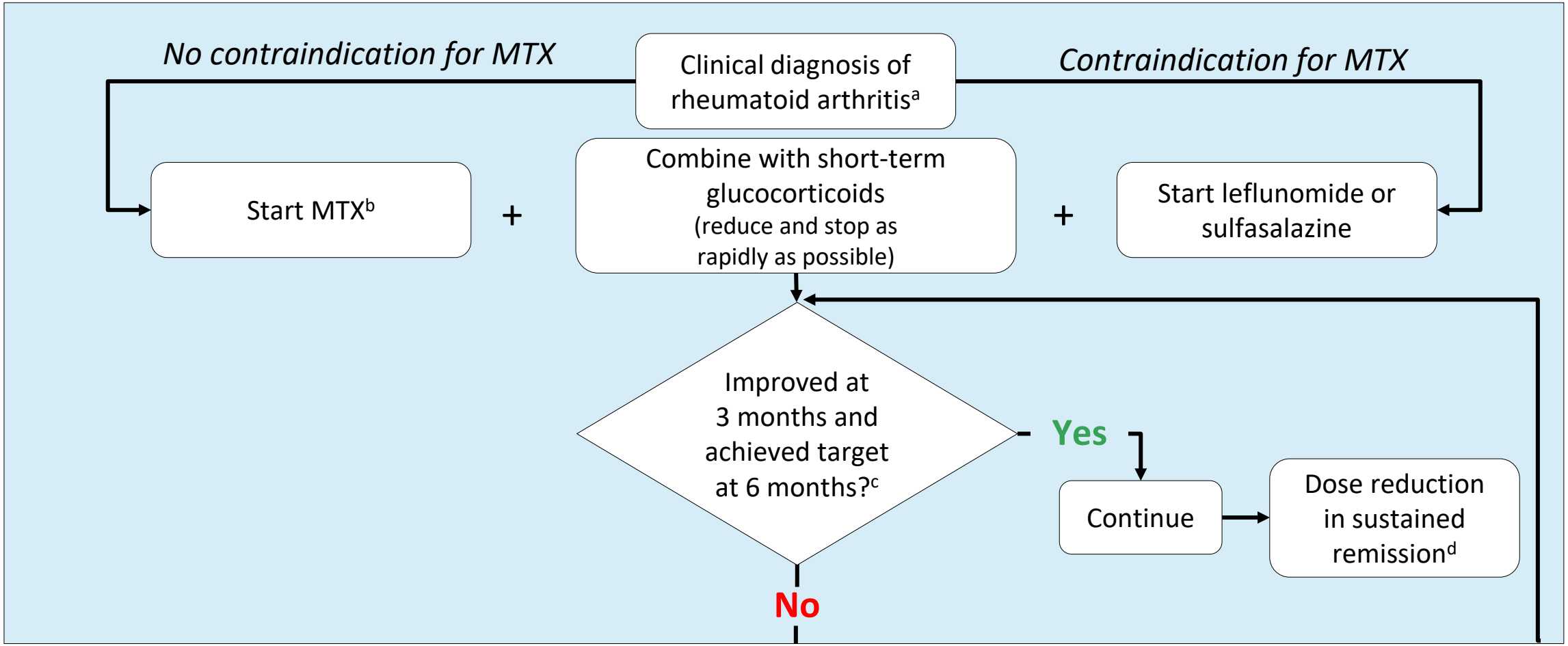
[a]The following risk factors for CV events and malignancies must be considered when intending to prescribe a JAK inhibitor: Age over 65 years; history of current or past smoking; other CV risk factors (e.g. diabetes, obesity, hypertension); other risk factors for malignancy (current or previous history of malignancy other than successfully treated non-melanoma skin cancer); risk factors for thromboembolic events (history of myocardial infarction or heart failure, cancer, inherited blood clotting disorders, or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery, or immobile).

bDMARD, biological disease-modifying antirheumatic drug; **csDMARD**, conventional synthetic disease-modifying antirheumatic drug; **CV,** cardiovascular; **DMARD**, disease-modifying antirheumatic drug; **EULAR**, European Alliance of Associations for Rheumatology; **JAK**, Janus kinase; **tsDMARD**, targeted synthetic disease-modifying antirheumatic drug

Smolen JS, et al. Ann Rheum Dis. 2023;82:3–18.

Recommendations: Phase 1

These recommendations can be applied for any patient at any point in time



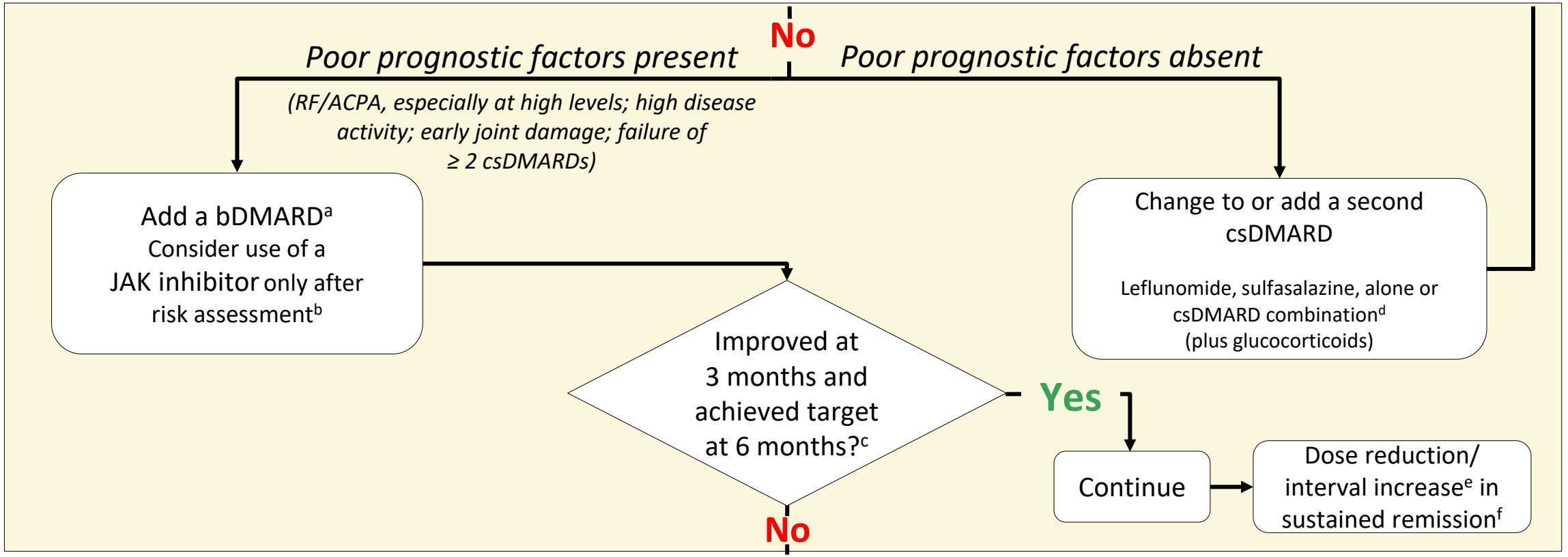
[a]2010 ACR-EULAR classification criteria can support early diagnosis. [b]"MTX should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with MTX does not exclude its use in combination with other csDMARDs, although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids. [c]The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (< 50% of disease activity) is seen after 3 months. [d]Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.

ACR, American College of Rheumatology; **csDMARD**, conventional synthetic disease-modifying antirheumatic drug; **EULAR**; European Alliance of Associations for Rheumatology; **MTX**, methotrexate

Smolen JS, et al. Ann Rheum Dis. 2023;82:3–18.

Recommendations: Phase 2

For insufficient responders to MTX and/or another csDMARD



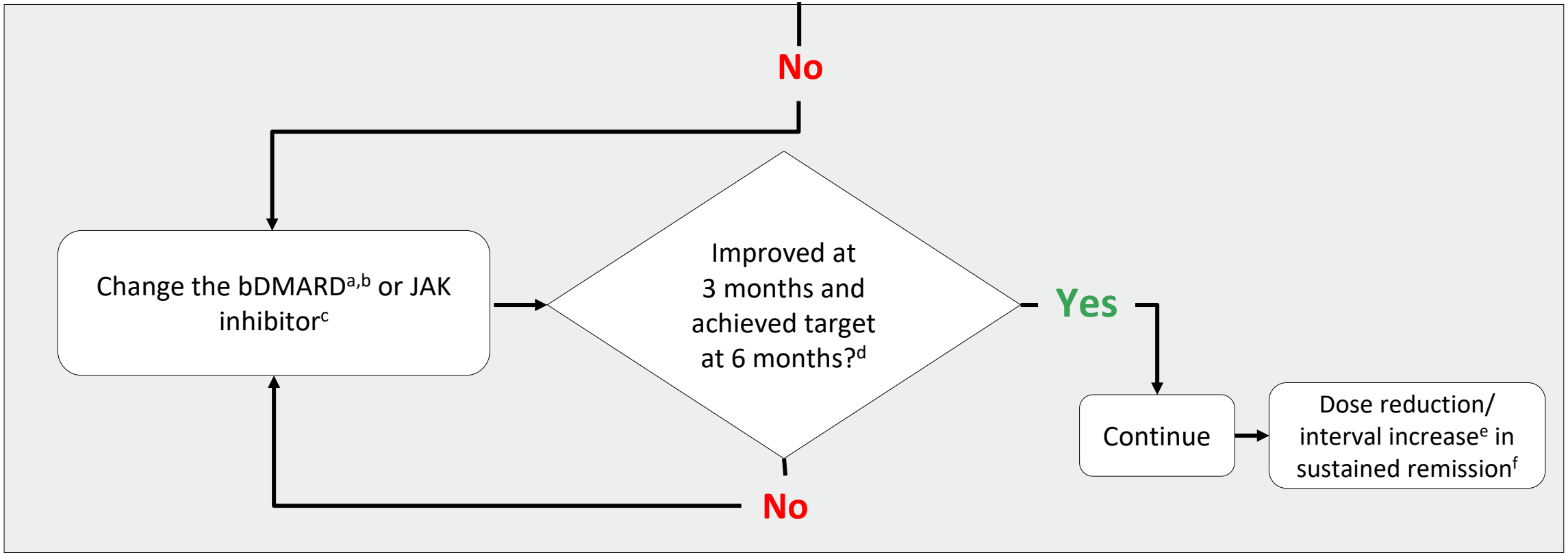
[a]Consider contraindications and risks. TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA-approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as co-medications, IL-6 inhibitors and tsDMARDs have some advantages. [b]The following risk factors for CV events and malignancies must be considered when intending to prescribe a JAK inhibitor: Age over 65 years; history of current or past smoking; other CV risk factors (e.g. diabetes, obesity, hypertension); other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC); risk factors for thrombotic events (history of MI or heart failure, cancer, inherited blood clotting disorders, or a history of blood clots, as well as patients taking combined hormonal oral contraceptive or hormone replacement therapy, undergoing major surgery, or immobile). [c]The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (< 50% of disease activity) is seen after 3 months. [d]The most frequently used combination comprises MTX, sulfasalazine, and hydroxychloroquine. [e]Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates. Most, but not all, patients can recapture their good state upon re-institution of the same bDMARD/tsDMARD, but before all this glucocorticoids must have been discontinued. [f]Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.

ACPA, anti-citrullinated protein antibodies; **ACR**, American College of Rheumatology; **bDMARD**, biological disease-modifying antirheumatic drug; **bsDMARD**, biosimilar disease-modifying antirheumatic drug; **csDMARD**; conventional synthetic disease-modifying antirheumatic drug; **CV,** cardiovascular; **EMA**, European Medicines Agency; **EULAR**; European Alliance of Associations for Rheumatology; **FDA,** Food and Drug Administration; **IL-6**, interleukin-6; **IL-6R**, interleukin-6 receptor; **JAK**, Janus kinase; **MI,** myocardial infarction; **MTX**, methotrexate; **NMSC**, non-melanoma skin cancer; **RF**, rheumatoid factor; **TNF**, tumour necrosis factor; **tsDMARD**; targeted synthetic disease-modifying antirheumatic drug

Smolen JS, et al. Ann Rheum Dis. 2023;82:3–18.

Recommendations: Phase 3

For insufficient responders to a bDMARD or JAK inhibitor



[a]Consider contraindications and risks. TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA-approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as co-medications, IL-6 inhibitors and tsDMARDs have some advantages. [b]From a different or the same class. [c]The following risk factors for CV events and malignancies must be considered when intending to prescribe a JAK inhibitor: Age over 65 years; history of current or past smoking; other CV risk factors (e.g. diabetes, obesity, hypertension); other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC); risk factors for thrombotic events (history of MI or heart failure, cancer, inherited blood clotting disorders, or a history of blood clots, as well as patients taking combined hormonal oral contraceptive or hormone replacement therapy, undergoing major surgery, or immobile). [d]The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (< 50% of disease activity) is seen after 3 months. [e]Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates. Most, but not all, patients can recapture their good state upon re-institution of the same bDMARD/tsDMARD, but before all this glucocorticoids must have been discontinued. [f]Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.

ACR, American College of Rheumatology; **bDMARD**, biological disease-modifying antirheumatic drug; **bsDMARD**, biosimilar disease-modifying antirheumatic drug; **csDMARD**; conventional synthetic disease-modifying antirheumatic drug; **CV**, cardiovascular; **EMA**, European Medicines Agency; **EULAR**, European Alliance of Associations for Rheumatology; **FDA,** Food and Drug Administration; **IL-6**, interleukin-6; **IL-6R**, interleukin-6 receptor; **JAK**, Janus kinase; **MI**, myocardial infarction; **NMSC**, non-melanoma skin cancer; **TNF**, tumour necrosis factor; **tsDMARD**, targeted synthetic disease-modifying antirheumatic drug

Smolen JS, et al. Ann Rheum Dis. 2023;82:3–18.

Measures of disease activity/remission in rheumatoid arthritis

Commonly used disease activity indexes and cut-offs

Scoring system	Formula	Disease activity state			
		Remission	Low	Moderate	High
SDAI	TJC28 + SJC28 + PtGA + EGA + CRP	≤ 3.3	> 3.3–11	> 11–26	> 26
CDAI	TJC28 + SJC28 + PtGA + EGA	≤ 2.8	> 2.8–10	> 10–22	> 22
DAS	Complex formula including Ritchie Articular Index, SJC44, ESR, and PtGA or GH	< 1.6	1.6–2.4	> 2.4–3.7	> 3.7
DAS28	Complex formula including TJC28, SJC28, ESR (or CRP), and PtGA or GH	< 2.6	2.6–3.2	> 3.2–5.1	> 5.1

Key differences

CDAI uses the same formula as SDAI, except CRP is not included

DAS28 is a modification of DAS, using only 28-joint counts

Both scores transform and weight their component variables, resulting in:

- Stronger influence of TJC than SJC
- High contribution of acute-phase reactant levels

DAS28 values calculated using CRP are lower than DAS28 values calculated using ESR

CDAI, Clinical Disease Activity Index; **CRP**, C-reactive protein (in SDAI in mg/dL); **DAS**, Disease Activity Score; **DAS28**, Disease Activity Score using 28-joint counts; **EGA**, Evaluator Global Assessment (Recommended format: a horizontal 10-cm Visual Analogue or Likert Scale with the best anchor and lowest score on the left side and the worst anchor and highest score on the right side); **ESR**, erythrocyte sedimentation rate; **GH**, general health (on a Visual Analogue Scale); **PtGA,** Patient Global Assessment; **SDAI**, Simplified Disease Activity Index; **SJC**, swollen joint count (the number indicates the number of joints taken into account); **TJC**, tender joint count (the number indicates the number of joints taken into account)

Anderson JK, et al. Arthritis Care Res (Hoboken). 2012;64:640–647.

Measures of disease activity/remission in psoriatic arthritis

Scoring system	Formula	Disease activity state			
		Remission	Low	Moderate	High
DAPSA	TJC68 + SJC66 + PtGA-VAS + Pain VAS + CRP	≤ 4	> 4–14	> 14–28	> 28
cDAPSA	TJC68+ SJC66 + PtGA-VAS + Pain VAS	≤ 4	> 4–13	> 13–28	> 28
CPDAI	Grades severity of involvement of 5 CPDAI domains (joints, skin, entheses, dactylitis, and spine), each scoring 0–3	< 2	3–4	5–6	> 7
PASDAS	TJC68 + SJC66 + PtGA-VAS + PhGA-VAS + LEI + dactylitis count + CRP + SF-36	< 1.9	> 1.9–≤ 3.2	> 3.2–5.4	> 5.4

cDAPSA uses the same formula as DAPSA, except CRP is not included

cDAPSA, clinical Disease Activity in Psoriatic Arthritis; **CPDAI,** Composite Psoriatic Disease Activity Index; **CRP,** C-reactive protein; **DAPSA,** Disease Activity in Psoriatic Arthritis; **LEI,** Leeds Enthesitis Index; **PASDAS,** Psoriatic Arthritis Disease Activity Score; **PhGA,** Physician Global Assessment; **PtGA,** Patient Global Assessment; **SF-36,** 36-item Short Form survey; **SJC**, swollen joint count (the number indicates the number of joints taken into account); **TJC**, tender joint count (the number indicates the number of joints taken into account); **VAS,** Visual Analogue Scale

Ogdie A, et al. Arthritis Care Res (Hoboken). 2020;72(Suppl 10):82–109.

Measures of disease activity/remission in ankylosing spondylitis[1]

Scoring System[1,2]	Formula	Disease activity state			
		Remission	Low	Moderate	High
ASDAS	Back pain + peripheral pain + morning stiffness duration + PtGA + CRP/ESR	≤ 1.3	> 1.4–2.0	> 2.1–3.4	≥ 3.5
BASDAI	Six patient-reported questions on fatigue, pain, swelling, discomfort, morning stiffness, and morning stiffness duration	≤ 2	> 2.1–3.0	> 3.1–3.6	≥ 3.7

ASDAS, Ankylosing Spondylitis Disease Activity Score; **BASDAI,** Bath Ankylosing Spondylitis Disease Activity Index; **CRP,** C-reactive protein; **ESR,** erythrocyte sedimentation rate; **PtGA,** Patient Global Assessment.

1. van der Heijde D, et al. Ann Rheum Dis. 2017;76:978–991. **2.** Salaffi F, et al. Health Qual Life Outcomes. 2014;12:129.

What does “remission” mean in rheumatology?

T2T algorithms for the treatment of rheumatoid arthritis,[1] psoriatic arthritis,[2] and ankylosing spondylitis[2,3] have been established and navigate our treatment options

- T2T aims at best to achieve minimal disease activity with biologic medicines, but can also aim next best to achieve low disease activity
- Parameters to measure these outcomes involve:
  - Reduction in swollen/tender joints from baseline after 12 weeks of continuous therapy; reduction in ESR and/or CRP, by 20% from baseline (ACR 20)
- Most of the drugs approved for use in rheumatology achieve ACR 20 response rates in the order of 80–90%
- It is harder to achieve response rates of ACR 50 and ACR 70 (usually 40% and 20%, respectively) across the majority of biologic medicines in rheumatology

ACR, American College of Rheumatology; **CRP,** C-reactive protein; **ESR,** erythrocyte sedimentation rate; **T2T,** treat-to-target

1. Smolen JS, et al. Ann Rheum Dis. 2023;82:3–18. **2.** Smolen JS, et al. Ann Rheum Dis. 2014;73:6–16. **3.** van der Heijde D, et al. Ann Rheum Dis 2017;76:978–991.

Super responders in rheumatological diseases??????

Rheumatoid arthritis

If seropositive for anti-CCP and RF

- Likely to respond to anti-TNF agents,[1] abatacept,[2] or rituximab[3]
- Enhanced response if patient has HLA haplotype specific for RA: HLA-DR4 haplotype[4]

If seronegative for anti-CCP and RF

- The response is less predictive and treatment failure or inadequate response is possible
- Usual practice is to start with an anti-TNF agent as long as no contraindication, and if lack of response by 6/12 or inadequate response, according to T2T paradigm, switch to a different mode of action[5]
  - JAKi if < 65 years and no contraindication, or tocilizumab or abatacept[5]
  - JAKi and tocilizumab can be used as monotherapy without MTX, so preferable to abatacept, which requires MTX as PBS requirement[6]

CCP, cyclic citrullinated peptide; **HLA**, human leukocyte antigen; **JAKi**, Janus kinase inhibitor; **MTX**, methotrexate; **PBS**, Pharmaceutical Benefits Scheme; **RA**, rheumatoid arthritis; **RF,** rheumatoid factor; **T2T,** treat to target; **TNF**, tumour necrosis factor

1. Julia A, et al. BMC Musculoskelet Disord. 2021;22:372. **2.** Kida D, et al. Sci Rep. 2020;10:19717. **3.** Kekow J, et al. Biologics. 2012;6:191-9. **4.** Wysocki T, et al. Cells. 2020;9:1127. **5.** Smolen JS, et al. Ann Rheum Dis. 2023;82:3–18. **6.** Abatacept Public Summary Document. November 2007. Available at: https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2007-11/pbac-psd-abatacept-nov07 (accessed August 2023)

Super responders in rheumatological diseases??????

Psoriatic arthritis and ankylosing spondylitis

- Response rates are a little more difficult to predict than in RA owing to lack of specific biomarkers to facilitate appropriate treatment response
  - Presence of HLA-B27 antigen in ankylosing spondylitis is helpful, but not a specific biomarker for treatment response
- The heterogeneity and numerous domains affected in these conditions can influence treatment response or lack thereof (skin, joints, nails, eyes, gut etc.)
- Usual practice is anti-TNF inhibitor first line, then IL-17 inhibitor or JAK inhibitor[1,2]

HLA, human leukocyte antigen; **IL-17**, interleukin-17; **JAK**, Janus kinase; **RA**, rheumatoid arthritis; **TNF**, tumour necrosis factor

1. Smolen JS, et al. Ann Rheum Dis. 2014;73:6–16. **2.** van der Heijde D, et al. Ann Rheum Dis 2017;76:978–991.

Remission vs super responder in rheumatology

- Remission aims for low disease activity in rheumatic diseases; to date, drug-free remission is not possible in rheumatological diseases, but dose tapering is a possibility
- We need to demonstrate a treatment response of 20% better than baseline to DHS to obtain ongoing approval of biologics for our patients
- Super responders do not really exist in rheumatic diseases owing to the lack of specific biomarkers to enhance and predict treatment response
- We have a lot of choice of biologics in rheumatology[1]
  - First-line choices have changed with the advent of new modes of action, convenience of dosing (tablet compared with SC or IV administration), and efficacy as monotherapy without MTX (40% incidence of MTX intolerance worldwide)
- Choice depends on patient disease burden, risk factors (CV, malignancy, infection risk, MS), needle phobia, domains to be addressed

CV, cardiovascular; **DHS,** Department of Human Services; **IV,** intravenous; **MS,** major surgery; **MTX**, methotrexate; **SC,** subcutaneous

1. Smolen JS, et al. Ann Rheum Dis. 2023;82:3–18.

Potential outcomes with biologics in rheumatology

- Improved function
- Off steroids
- Off methotrexate
- Back to work
- Life changing

History of biologics in rheumatology in Australia

- **2003:** TGA approval of TNFi adalimumab
- **2006:** advent of IV infliximab for RA, PsA, and AS on PBS; TGA approval of etanercept for the same indications
- SC administration in 2 formulations for each agent: pen or prefilled syringe
- Newer TNFis: golimumab, certolizumab pegol (useful in pregnancy)
- **March 2021**: adalimumab citrate-free (injection is less painful; increased compliance)
- Biosimilars for adalimumab, etanercept, infliximab
- JAK inhibitors with oral administration (increased risk of MACE, thrombosis AE, now has a boxed warning)
- IV tocilizumab, IV abatacept, followed by SC formulations to reduce the need for hospital in the home and infusion centres, which are less convenient and more costly to patients (need to pay excess)
- **2018:** newer agents ustekinumab, secukinumab, guselkumab for PsA and AS

AE, adverse event; **AS**, ankylosing spondylitis; **IV**, intravenous; **JAK**, Janus kinase; **MACE**, major adverse cardiovascualr events; **PBS**, Pharmaceutical Benefits Scheme; **PsA**, psoriatic arthritis; **RA**, rheumatoid arthritis; **SC**, subcutaneous; **TGA**, Therapeutic Goods Administration; **TNFi**, tumour necrosis factor inhibitor

Fletcher A et al. Rheumatology (Oxford). 2022;61:3939–3951.

Advantages of SC administration over IV

Patient can be trained to self-administer;
no need for ongoing nurse or GP support

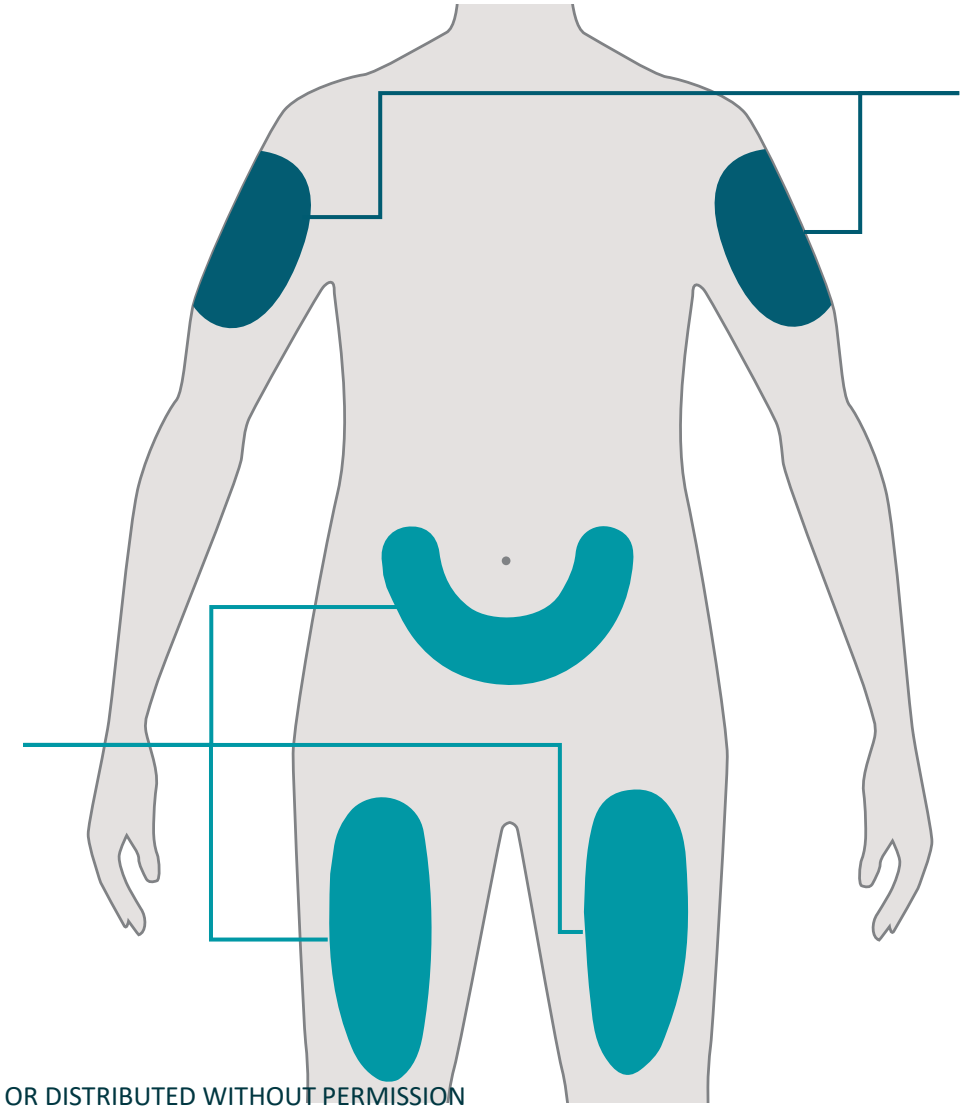
In early days, GPs did first 3 injections to determine allergy

In clinical trials, very low risk of allergic response

GP, general practitioner; **IV,** intravenous; **SC,** subcutaneous

Injection sites

Alternatively, another person can inject in your upper arm



Inject yourself in thighs or abdomen

Issues with IV administration

- Need hospital appointment/provider number for PBS approval
- Need IV access (portacath in some)
- Hospital in the home: can do it if private insurance
  - If no private insurance, need to refer to public hospital infusion centre

However, IV better for patients with joint deformities or needle phobias

IV, intravenous; **PBS**, Pharmaceutical Benefits Scheme

Strategies to support patients' transition to SC administration

- Teach them or their partner how to inject (Nurse Support Programme, GP, or specialist)
- Make it easy to use re device, and hurt less (room temp before admin)
- Check compliance with 6-month recall review and check status of repeats
- Pharma nurse support programmes set up reviews for rheumatologists who enrolled their patients on their biologic
  - Called patients 4 weeks before last repeat filled and checked they were to do bloods before scheduled review
    - Helped us out a lot on admin side
    - *Only one pharma company still doing this*

GP, general practitioner; **pharma**, pharmaceutical; **SC**, subcutaneous

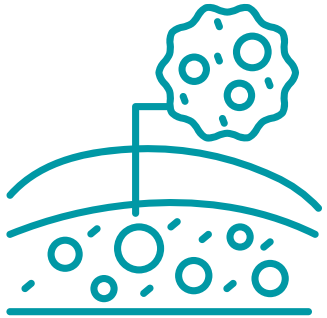
Monitoring on biologics in rheumatology: pre-biologic screening

- QuantiFERON-TB
- Hepatitis B and C
- Lupus autoantibodies
- Neurological disorders
- Herpes zoster risk and vaccination
  - Mandatory to have Shingrix before JAKi in USA

JAKi, Janus kinase inhibitor; **TB**, tuberculosis; **USA**, United States of America

Monitoring on biologics in rheumatology

- Infection risk
- Reactivation of TB
- Demyelination
- Lymphoma
- NMSC
- Melanoma
- Malignancy
- NO LIVE VACCINES
- Pregnancy and breastfeeding



NMSC, non-melanoma skin cancer; **TB**, tuberculosis

Issues with biologics in rheumatology

- Increased paperwork for application via DHS
- Need for a biologics nurse, but not viable in solo private practice
- COVID-related issues and immunosuppression
- Stopping biologic around surgery to reduce risk of infection
- Travelling with these drugs and keeping them cold!

COVID, coronavirus disease; **DHS**, Department of Human Services

THANK YOU FOR YOUR ATTENTION

ADVENT
TYPE 2 INFLAMMATORY DISEASES

REMISSION
OR
SUPER RESPONDER

SPECIAL TWO PART SERIES

Comorbidities that may affect response to biologics

A/Prof Joy Lee

Lead of the Asthma and Allergy Unit at the Austin Hospital and consultant at Alfred Hospital Asthma, Allergy and Immunology Department and the Allergy Unit at Monash Medical Centre

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

SPEAKER

A/Prof Joy Lee

Lead of the Asthma and Allergy Unit at the Austin Hospital and consultant at Alfred Hospital Asthma, Allergy and Immunology Department and the Allergy unit at Monash Medical Centre

Associate Professor Joy Lee completed her basic medical training at the University of Auckland, New Zealand. She completed her basic physician training at the Alfred Hospital with further advanced training at Monash Medical Centre and St Vincent's Hospitals. In 2016 she completed a dedicated fellowship in Severe Asthma and Allergy at the Alfred Hospital, Melbourne. She is a current PhD candidate undertaking research in difficult asthma with the School of Public Health and Preventive Medicine at Monash University. Her research has focused on improving asthma inhaler usage, difficult-to-control asthma and epidemic thunderstorm asthma. A/Prof Lee is also an investigator in clinical trials for therapies for asthma and allergic nasal disease.

Disclosures

Joy Lee has received speaker honoraria from Sanofi, Astra Zeneca, Inside Practice and the Limbic.

She has received travel grants from Sanofi and GSK.

Disclaimer

This case study was selected by Joy Lee independently of the sponsor

It gives general information on treatment considerations based on recent data and the individual case study. The presenter is providing their own experiences.

Nothing in this presentation should be construed as medical advice since each patient is different.

Since each patient is an individual case, you should use your own medical judgement to choose the appropriate treatment for each patient.

This presentation contains discussion around potential off-label use of medications e.g., erythromycin, esomeprazole 40 mg BD, flecainide 100 mg PRN and ranitidine 150 mg BD (now suspended from ARTG). Sanofi does not endorse the off-label use of medications.

Mrs Y, 79-year-old female

Sept 2016

- Presents with cough, sputum, chest tightness, exertional dyspnoea
- Reports progressive symptoms over past few months
- Previously able to walk substantial distances on the flat
- Now SOB going a few 100 m or up a flight of stairs
- Symptoms not always responsive to salbutamol, still using this four times a day with spacer
- 2 x previous CT chest – no bronchiectasis, mucus plugging

CT, computed tomography; **SOB**, shortness of breath; **LLL**, left lower lobe

Stock image – not real patient used for illustrative purposes only

Asthma history

- Asthma diagnosed in childhood - “sickly child”
- Recalls getting IM cortisone
- No previous ICU or hospitalisation
- Good asthma control in her 20s/early adult years
- Asthma triggers: allergen exposures, cold air, exertion
- Variable ICS/LABA adherence budesonide/formoterol 200/6 two puff BD (50-75% adherent), ciclesonide 160 mcg two puffs daily (only taking twice a week)
- In last 12 months: 4 courses Abx and OCS for infective exacerbations
- Also has trialled several weeks of erythromycin*, bisolvon - no improvement
- Has seen a respiratory physiotherapist for airway clearance

***Disclaimer: off-label use**

IM, intramuscular; **ICU**, intensive case unit; **ICS**, inhaled corticosteroid; **LABA**, long-acting β2-agonist; **BD**, twice-daily; **Abx**, antibiotics; **OCS**, oral corticosteroids

Social history

- Born in Australia, Greek descent
- Retired retail shop owner, part-time volunteer and language interpreter
- Enjoys travelling with her husband, especially cruises
- Never smoked
- No history of AERD

AERD; aspirin-exacerbated respiratory disease

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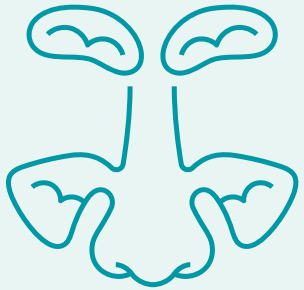
Other medical history

Allergic rhinitis and chronic sinusitis

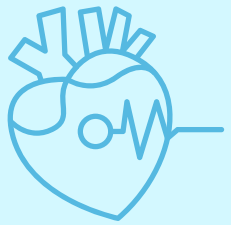
Tonsillectomy in childhood



Hypertension

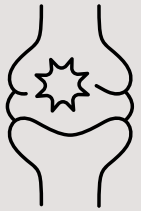
Paroxysmal atrial fibrillation

Ischaemic heart disease



Osteoarthritis

Osteoporosis



Anxiety

Gastroesophageal reflux disease (GORD)

Lactose malabsorption

Irritable bowel syndrome

Medications list

- Candesartan 8 mg daily
- Diltiazem 60 mg twice daily
- Simvastatin 20 mg nocte
- Warfarin as per INR (later swapped to rivaroxaban)
- Esomeprazole 40 mg twice daily*
- Ranitidine 150 mg BD†
- Paracetamol, codeine PRN
- B_{12} injections
- Folic acid twice weekly
- Cholecalciferol 25 µg daily

***Disclaimer: off-label use; †suspended from ARTG**

PRN, as needed; **BD**, twice-daily; **INR**, international normalised ratio; **nocte**, nightly

Clinical examination and investigations

- SpO_2 97%
- HR 82 bpm
- BMI 34.3 kg/m^2
- Occasional inspiratory wheeze
- No visible nasal polyps
- Mallampatti Grade 3

- FEV_1 1.58 L 10% BD change
- FVC 2.2 L 11% BD change
- FER 71%
- SPT HDM 9 mm, cat dander 4 mm
- CRP 24 mg/L
- IgA, IgG, IgM normal, IgE 1000 IU/mL
- EOS 0.23 x 10^9/L
- RAST *Aspergillus* negative, precipitins negative

SpO_2, saturation of peripheral oxygen; **HR**, heart rate; **BMI**; body mass index; **FEV_1**, forced expiratory volume in 1 second; **FVC**, forced vital capacity; **FER**, forced expiratory ratio; **BD**, bronchodilator; **SPT**, skin prick test; **HDM**, house dust mite; **CRP**, C-reactive protein; **EOS**, eosinophils; **RAST**, radioallergosorbent test; **IgA**, immunoglobulin A; **IgG**, immunoglobulin G; **IgM**, immunoglobulin M

Investigations

- CT sinus
- Deviated nasal septum
- Mucosal thickening maxillary sinus
- Air fluid level sphenoid sinus
- Opacification ethmoid sinus

- Started sinus rinse and intranasal steroid irrigation, referred to ENT
- Airway clearance
- Peak flows 250-350 mL
- Commenced LAMA (tiotropium 2 puff daily)

CT; computed tomography; **ENT**, ear, nose and throat; **LAMA**, long-acting muscarinic antagonist

Progress 2017

Sept 2016 | 2017

- One exacerbation
- Active GORD symptoms
- Repeat CT chest – LLL mucus plugging now progressed to LLL bronchiectasis
- Reduction in FEV_1, 12% BD reversibility
- Commenced azithromycin* 500 mg MWF and referred to difficult asthma protocol
- Non-adherent to sinus rinses, airway clearance exercises

***Disclaimer: off-label use**

CT; computed tomography; **GORD**, gastro-oesophageal reflux disease; **LLL**, left lower lobe; **FEV_1**, forced expiratory volume in 1 second, **BD**, bronchodilator; **MWF**, Monday, Wednesday, Friday

Stock image – not real patient used for illustrative purposes only

Exacerbation 2017, required hospitalisation

Spirometry:
FER 51
FEV_1 59%
FVC 86%
15% and less than 200 mL reversibility

IV antibiotics
Physiotherapy review and airway Clearance regimens

FEV_1, forced expiratory volume in 1 second; **FVC**, forced vital capacity; **FER**, forced expiratory ratio; **IV**, intravenous

Stock image – not real patient used for illustrative purposes only

Progress

- Noted significant improvements in reduction in sputum burden on azithromycin* and post-tune-up
- Also completed a course of pulmonary rehabilitation
- Repeat spirometry
  - FER 62
  - FEV_1 81%
  - FVC 95%
  - no significant BDR
- Repeat bloods
  - EOS 0 x 10^9/L
  - ANCA indeterminate
  - negative MPO and PR3
  - BNP 99 pg/mL
  - Normal Vit D
  - ANA 1:320
  - Total IgE 124 IU/mL
  - RAST HDM score 4
- Biologics discussed, patient thought to be ‘too well’, ACQ 1.2

***Disclaimer: off-label use**

FEV_1, forced expiratory volume in 1 second; **FVC**, forced vital capacity; **FER,** forced expiratory ratio; **BDR**; bronchodilator reversibility; **EOS**, eosinophils; **ANCA**, antineutrophilic cytoplasmic antibody; **MPO**, myeloperoxidase; **PR3**, proteinase 3; **BNP**, brain/B-type natriuretic peptide; **ANA**, antinuclear antibodies; **IgE**, immunoglobulin E; **RAST**, radioallergosorbent test; **HDM**, house dust mite; **ACQ**, asthma control questionnaire

End 2017

Sept 2016 | 2017 | **End 2017**

- 3 exacerbations requiring OCS
- Significant anxiety
- Underwent fundoplication for GORD
  - on PPI – helped GORD symptoms ++
- ACQ-5 2.4
- Eosinophils 0.6 x 10^9/L
- Application for omalizumab sent

OCS, oral corticosteroids; **FEV_1**, forced expiratory volume in 1 second; **ACQ**, asthma control questionnaire; **GORD**, gastro-oesophageal reflux disease; **PPI**, proton pump inhibitor

Stock image – not real patient used for illustrative purposes only

Mid-2018

Sept 2016 | 2017 | End 2017 | **Mid 2018**

- Diagnosed with PMR by rheumatologist and commenced prednisolone 10 mg daily, intra-articular steroid injections given, methotrexate added
- Lung function best ever: FEV_1 115% no BDR
- ACQ 0.8
- Omalizumab applied but patient reluctant and feeling well so did not commence
- Azithromycin* ceased, ciclesonide ceased
- Seen by sleep clinic – mild OSA, severe in supine REM, weight loss recommended

***Disclaimer: off-label use**

PMR; polymyalgia rheumatica; **FEV_1**, forced expiratory volume in 1 second; **BDR**, bronchodilator responsiveness; **ACQ**, asthma control questionnaire; **OSA**, obstructive sleep apnoea; **REM**; rapid eye movement

Stock image – not real patient used for illustrative purposes only

2019

Sept 2016 | 2017 | End 2017 | Mid 2018 | **2019**

- Went on a cruise and became unwell while travelling
- Had a CTPA – no PE
- Recurrence of sputum – productive cough, dyspnoea
- FEV_1 drop to 85% with 15% reversibility
- Ciclesonide restarted, azithromycin* restarted
- Repeat CT chest – no bronchiectasis
- ACQ 4.2 – treated with antibiotics and OCS (increased from baseline dose of 5 mg for PMR)
- Reapplied for omalizumab (IgE > 1000 IU/mL)

***Disclaimer: off-label use**

CTPA; CT pulmonary angiogram; **PE**, pulmonary embolism; **CT**, computed tomography; **FEV_1**, forced expiratory volume in 1 second; **OCS**, oral corticosteroids; **ACQ**, asthma control questionnaire; **PMR**; polymyalgia rheumatica; **IgE**, immunoglobulin E

Stock image – not real patient used for illustrative purposes only.

Mid-late 2019

Sept 2016 | 2017 | End 2017 | Mid 2018 | 2019 | **Late 2019**

- OCS withheld prior to spirometry and FEV_1 dropped to 59%
- Commenced omalizumab 375 mg SC fortnightly

OCS, oral corticosteroids; **FEV_1**, forced expiratory volume in 1 second; **SC**, subcutaneous

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Jan 2020

Jan 2020

- Three months of omalizumab
- ACQ-4 -> 2.2
- Went on another cruise and could walk on the day trips with improved exercise capacity
- OCS reduced 7 mg >> 3 mg daily
- FEV_1 improved to 86% but still 15% BDR
- Self-reduced budesonide/formoterol to once daily and stopped ciclesonide
- No exacerbations

OCS, oral corticosteroids; **FEV_1**, forced expiratory volume in 1 second; **BDR**; bronchodilator reversibility; **ACQ**, asthma control questionnaire

Stock image – not real patient used for illustrative purposes only

2020

- Phone reviews mid-COVID pandemic
- ACQ now 0.6 -1.2
- No exacerbations during lockdowns of 2020
- No spirometry available

ACQ, asthma control questionnaire; **COVID;** coronavirus

2021

Jan 2020 | 2021

- 3 x Exacerbations: Cough and sputum and three courses OCS up to 25 mg
- Taught how to self-administer omalizumab
- Adherent to ICS/LABA
- Got a treadmill to walk on at home – up to 2.5 km daily
- No need for SABA during exercise
- Treated for osteoporosis with IV bisphosphonate after dental clearance
- Can’t reduce OCS to < 3 mg due to PMR and asthma symptoms
- Discussed switching omalizumab to dupilumab

ICS, inhaled corticosteroid; **LABA**, long-acting β2-agonist; **BD**, twice-daily; **OCS**, oral corticosteroids; **SABA**, short-acting β2-agonist; **PMR**; polymyalgia rheumatica; **IV**, intravenous

2022

Jan 2020 | 2021 | **2022**

- Ongoing symptoms, ACQ 3.8
- EOS 0 x 10^9/L, CRP 16 mg/L, WCC 8 x 10^9/L
- Using SABA nebulisers four times a day
- Unable to travel
- CT chest – minimal bibasal atelectasis and mild bronchiectasis
- Had COVID in Feb and had to increase prednisolone during this
- Spirometry: FEV_1 90%, FeNO 48 ppb
- Commenced dupilumab June 2022

SABA, short-acting β2-agonist; **EOS**, eosinophils; **CT**, computed tomography; **FEV_1**, forced expiratory volume in 1 second; **OCS**, oral corticosteroids; **ACQ**, asthma control questionnaire; **PMR**; polymyalgia rheumatica; **WCC**, white cell count; **CRP**, C-reactive protein; **COVID;** coronavirus; **FeNO**; fractional exhaled nitric oxide

2023: 6 months later

Jan 2020 | 2021 | 2022 | **2023**

- Transient mild eosinophilia 0.1 > 0.4 > 0.6 > 0.4 > 0.1 x 10^9/L
- Noted less dyspnoea, less sputum
- Weaned off all OCS (previously on baseline 5-7 mg)
- ACQ 1.8
- FEV_1 97%
- FeNO 14 ppb

FEV_1, forced expiratory volume in 1 second; **OCS**, oral corticosteroids; **ACQ**, asthma control questionnaire; **FeNO**; fractional exhaled nitric oxide

Stock image – not real patient used for illustrative purposes only

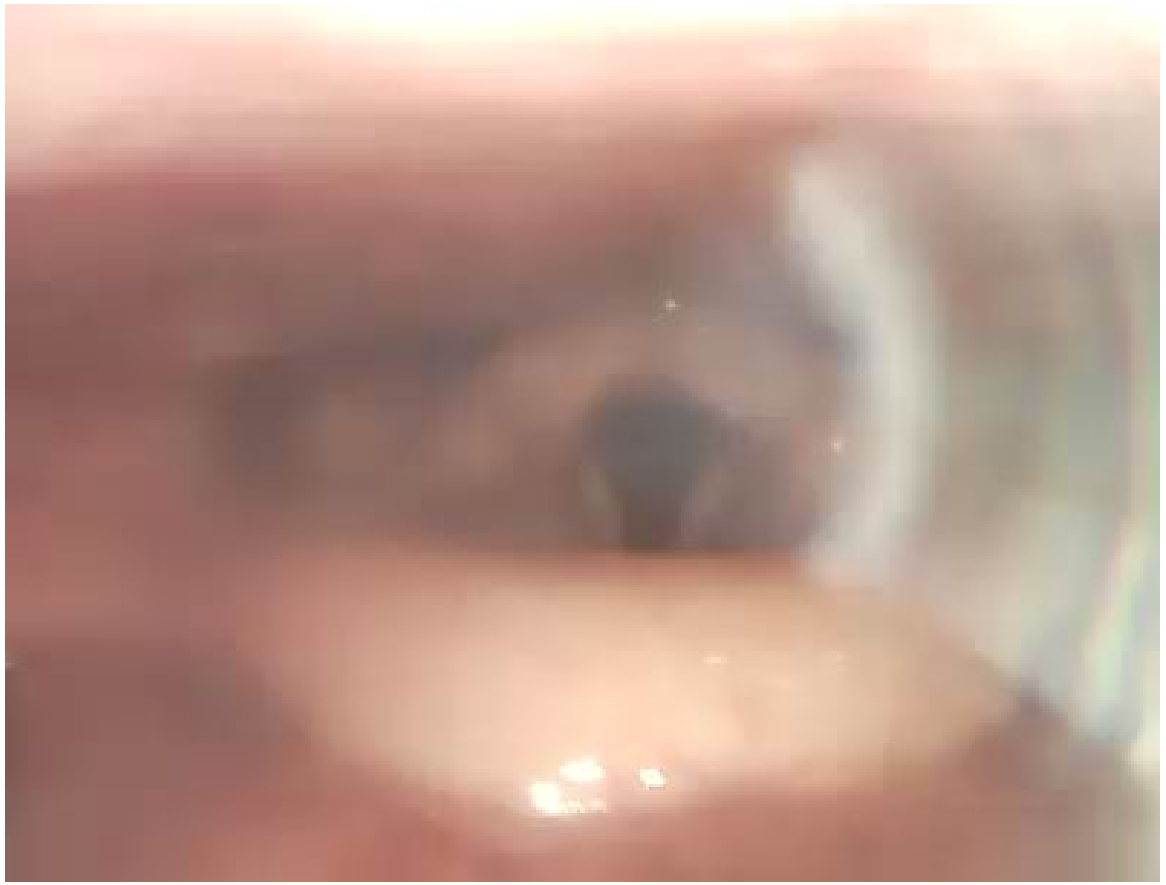
HOWEVER, over last 6 months…

- 1 x exacerbation requiring OCS
- Coughing, sensation of mucus/lump in throat
- Throat clearing frequently
- Loss of voice, worse if stressed, breathless with talking
- Throat tightness leading to dyspnoea
- Uncontrolled reflux symptoms
- Symptoms can be triggered by strong-smelling cleaning products
- Can’t volunteer/interpret due to voice issues

OCS, oral corticosteroids

Proceeded to odour provoked laryngoscopy

- Nasoendoscopy pre- and post- Glen20
- Post exposure: increased paradoxical vocal cord adduction compared to baseline, sensation of mucus in throat (none visualised on scope), cough, some voice change
- VCD thought likely

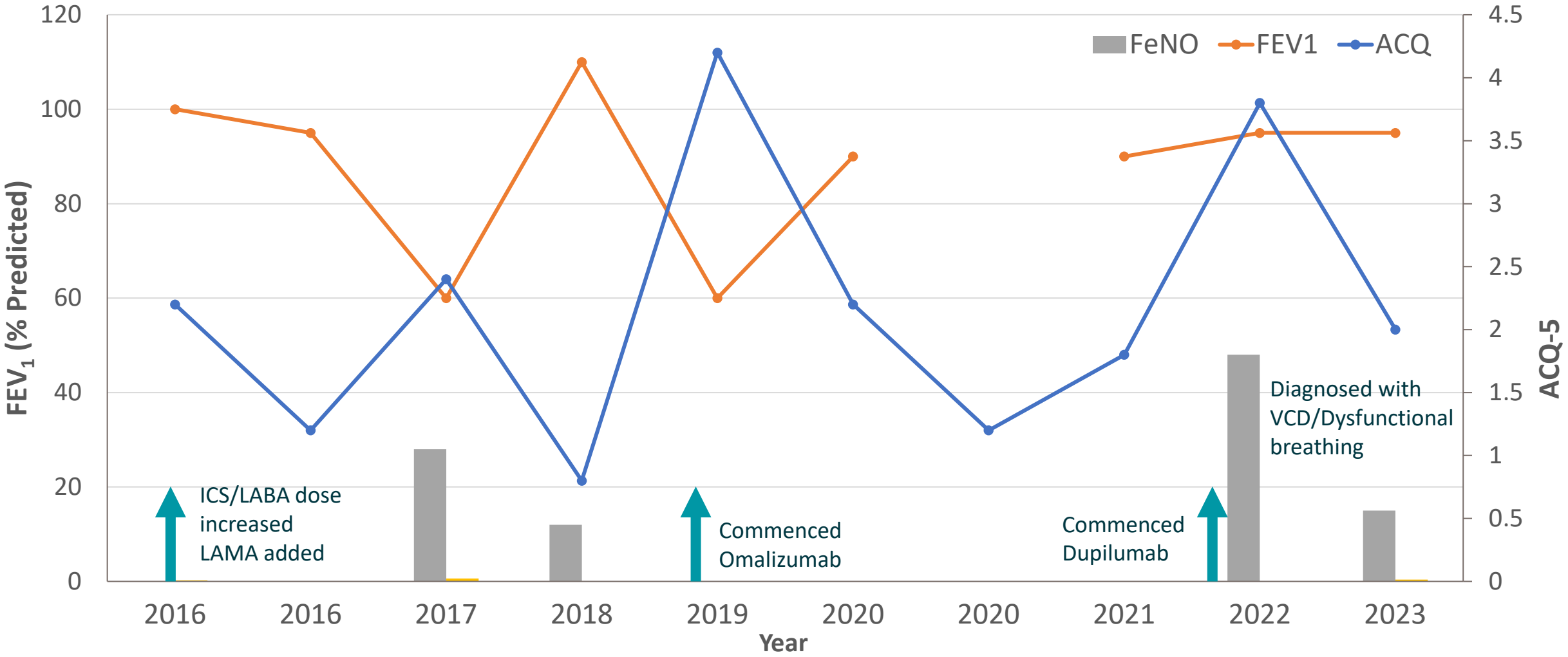


Video from clinical practice, used with permission. Not to be copied

VCD, vocal cord dysfunction

- Referred to speech pathologist
- Esomeprazole increased to 40 mg daily
- Reminded to restart intranasal treatments (had been less adherent)

Trends in ACQ, FEV_1, FeNO



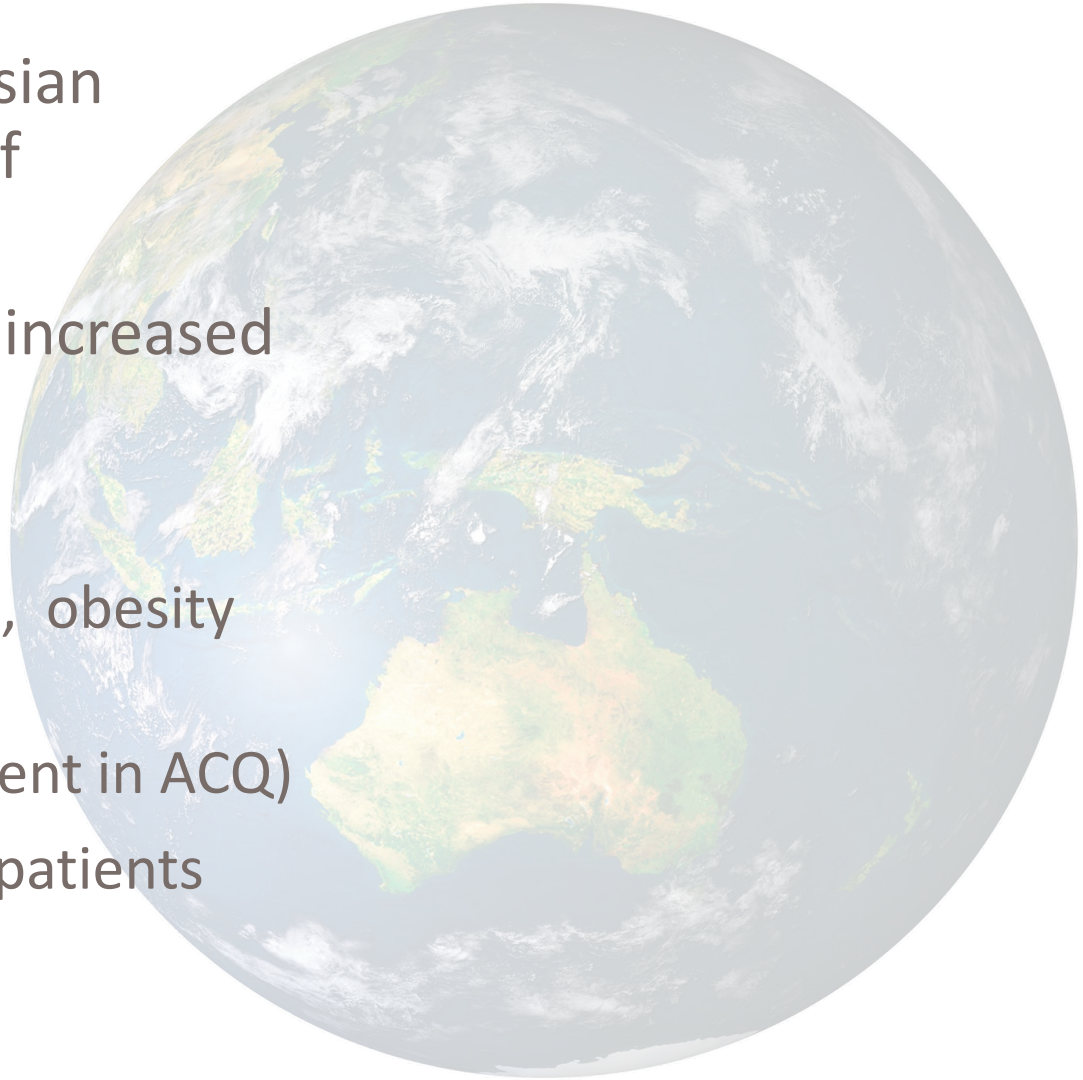
ICS, inhaled corticosteroid; **LAMA**, long-acting muscarinic antagonist; **LABA**, long-acting β2-agonist; **FeNO**, fractional exhaled nitric oxide; **FEV_1**, forced expiratory volume in 1 second; **ACQ**, asthma control questionnaire

Do comorbidities affect response to biologics?

- Analysis currently underway of the Australasian Severe Asthma Registry regarding impacts of comorbidities and response to biologics
- Fewer comorbidities are associated with an increased chance of achieving asthma remission[1]

Australian Xolair Registry[2]

- 95% had one or more comorbidities (rhinitis 48%, obesity 45%, cardiovascular disease 23%)
- 83% responded based on PBS criteria (improvement in ACQ)
- ACQ-5 reduced to 0.75 (well controlled) in 1 in 5 patients
- Reduced OCS



OCS, oral corticosteroid; **ACQ**, asthma control questionnaire; **PBS**, Pharmaceutical Benefits Scheme

1. Westerhof GA, et al. J Allergy Clin Immunol. 2018;141(1):104-9.e3. **2**. Gibson PG, et al. Int Med J. 2016;46(9):1054-62.

Super responders in severe asthma[1]

Mepolizumab effectiveness and identification of super-responders in severe asthma

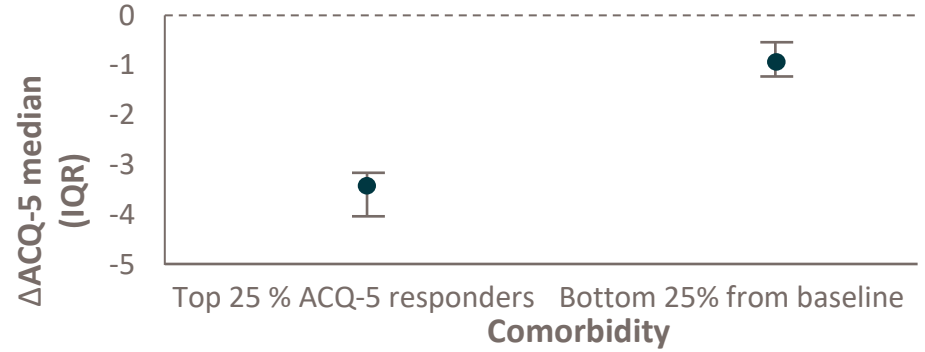
Harvey ES et al. Eur Respir J. 2020;55(5)

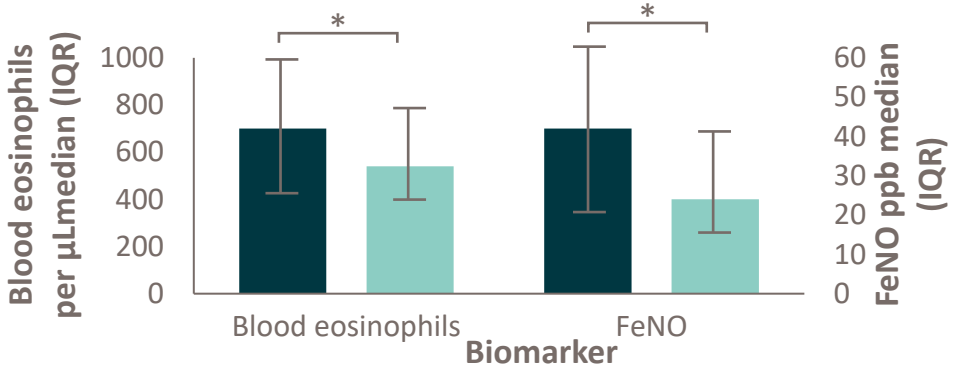
"Super-Responder" = Achieve significant reductions in ACQ and well-controlled asthma after 6 months

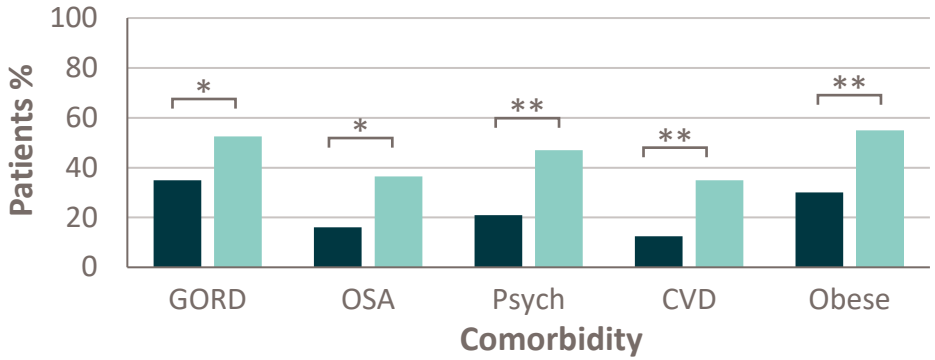
Median ACQ -5 score reduction of -3.4

Predominantly :

- Female (67% vs 43%, p=0.005)
- Lower BMI kg/m^2 (median 27.8 vs 31, p=0.006)
- Shorter duration of asthma (median 23.6 vs 34.1 yrs, p=0.037)
- Higher baseline blood EOS (median 700 vs 535 cells/µL, p=0.044)
- Higher baseline FeNO (FeNO 41 vs 23 ppb, p=0.026)
- Higher baseline ACQ-5 (median 4.2 vs 3.0, p<0.001)
- Less likely to be on OCS
- More likely to have CRSwNP/fewer comorbidities
- Less likely to have: OSA, GORD, psychiatric disorders, CV disease







*p <0.05; **p <0.01

1. Harvey ES, et al. Eur Respir J. 2020;55(5).

Long-Term Therapy Response to Anti-IL-5 Biologics in Severe Asthma-A Real-Life Evaluation

Eger K, et al. J Allergy Clin Immunol Pract. 2021;9(3):1194-200.

What is already known about this topic? Real-life data about long-term effects of anti–IL-5 treatment in patients with severe asthma are limited. Many questions about super responders and nonresponders, predictors of response, and residual disease manifestations are still unanswered.
What does this article add to our knowledge? In real-life, a small proportion of patients with specific characteristics show super response to long-term anti–IL-5 treatment. Most partial responders show impaired lung function or uncontrolled sinonasal disease, causing physicians to switch between biologics.
How does this study impact current management guidelines? Although anti–IL-5 biologics effectively reduce asthma exacerbations and oral glucocorticoid use in patients with eosinophilic asthma, in real-life many patients continue to suffer from bothersome disease manifestations despite anti–IL-5 treatment and these may require additional therapies.

After 2 years of anti–IL-5 treatment:

- 14% of patients were super responders
- 69% partial responders and
- 11% non-responders

- Super response was predicted by shorter asthma duration and higher FEV_1, and tended to be associated with adult-onset asthma, absence of nasal polyps, and lower body mass index

Eger K, et al. J Allergy Clin Immunol Pract. 2021;9(3):1194-200.

A systematic and treatable traits approach beyond biologics may help to improve outcomes[1]

- Previous studies have identified an average of 10 treatable traits in severe asthma patients[2]
- Targeting just type 2 airway inflammation may be insufficient to achieve full asthma control
- Comorbidities/traits of:
  - obstructive sleep apnoea
  - vocal cord dysfunction
  - inhaler device polypharmacy and non-adherence
  - upper airway disease
  - physical inactivity and obesity
  - systemic inflammation
  - anxiety and depression
- were all independently associated with increased asthma exacerbations[1,2]

1. Hiles SA, et al. J Allergy Clin Immunol. 2021;9(3):1255-64.e2. **2**. McDonald VM, et al. Respirology. 2019;24(1):37-47.

Clinical Asthma Remission Obtained with Biologics in Real Life: Patients' Prevalence and Characteristics

Sposato B, et al. J Pers Med. 2023;13(6):1020

In this study:

- 21.8% (omalizumab)
- 23.6% (mepolizumab)
- 35.8% (benralizumab) and
- 23.5% (dupilumab) were able to achieve clinical remission

In patients treated with omalizumab:

- Older age
- Higher BMI
- A later age of asthma onset
- Sinusitis/nasal polyposis
- Hypertension and chronic heart disease presence
- Higher exacerbation baseline

predicted failure to achieve asthma remission

1. Sposato B, et al. J Pers Med. 2023;13(6):1020

Take home messages

- Comorbidities commonly exist among patients with severe asthma and can affect response to biologics
- Presence of some comorbidities may predict greater response
  - e.g., CRSwNP, atopic dermatitis and dupilumab
- Presence of other comorbidities predict poorer response or less likely to achieve clinical remission
  - e.g., obesity, older age, history of smoking, ILO, anxiety, depression**In some studies*
- Screening with a systematic/treatable traits approach for the presence of comorbidities so targeted treatment can be arranged to complement biologics is important to increase the chance of the best clinical response

CRSwNP, chronic rhinosinusitis with nasal polyps; **ILO**, inducible laryngeal obstruction

Prescribing Information

PBS Information: Refer to PBS schedule for full authority information. Authority required for patients aged ≥12 years with chronic severe atopic dermatitis and uncontrolled severe asthma. This product is not listed on the PBS for infants aged 6 months to 5 years severe atopic dermatitis, children 6 to 11 years of age with severe atopic dermatitis or moderate to severe asthma, or for patients with uncontrolled chronic rhinosinusitis with nasal polyps.

Dupilumab PBS Information: Refer to PBS schedule for full authority information. Authority required for patients aged ≥12 years with chronic severe atopic dermatitis and uncontrolled severe asthma. This product is not listed on the PBS for children 6 to 11 years of age with severe atopic dermatitis or moderate to severe asthma, or for patients with uncontrolled chronic rhinosinusitis with nasal polyps.

Please review full Product Information before prescribing. Full Product Information is available from sanofi-aventis australia pty ltd at http://www.guildlink.com.au/gc/ws/sw/pi.cfm?product=swpdupix or by contacting 1800 818 806 or by scanning the QR code below.

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

Date of preparation | August 2023 | MAT-AU-2301876

ADVENT
TYPE 2 INFLAMMATORY DISEASES

REMISSION OR SUPER RESPONDER

SPECIAL TWO PART SERIES

Case 2: Improving but not a super responder: should we switch treatments?

Prof Mark Hew

Head of Allergy, Asthma & Clinical Immunology
The Alfred Hospital,
Melbourne

RESPIRATORY ADVENT ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

SPEAKER

Prof Mark Hew

Head of Allergy, Asthma & Clinical Immunology, the Alfred Hospital; Clinical Professor, School of Public Health & Preventive Medicine, Monash University.

Mark qualified in Medicine at Melbourne in 1995. Following specialist respiratory training, he undertook a fellowship in severe asthma at the Royal Brompton Hospital and National Heart & Lung Institute in London. He received his PhD from Imperial College London and later completed a Masters in Evidence-Based Health Care at Oxford. Mark heads Allergy, Asthma & Clinical Immunology services at the Alfred Hospital and holds research affiliations with both Melbourne and Monash Universities. His interests include difficult asthma, allergic disease, pleural medicine, and endo-bronchial ultrasound.

Disclosures

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- GlaxoSmithKline
- AstraZeneca
- Sanofi
- Novartis
- Teva

All payments were made to his employer, Alfred Health

Disclaimer

This case study was selected by Mark Hew independently of the sponsor

It gives general information on treatment considerations based on recent data and the individual case study. The presenter is providing their own experiences

Nothing in this presentation should be construed as medical advice since each patient is different

Since each patient is an individual case, you should use your own medical judgement to choose the appropriate treatment for each patient

Difficult asthma protocol evaluation in 2016

- 59 years old, asthma since age 43 years, ex-smoker
- ACQ score 3.6
- 8 exacerbations in past 12 months
- Budesonide, beclomethasone, tiotropium, montelukast
- Frequent reliever use
- FEV_1 1.51 (62% predicted) with 25% reversibility

- Chronic rhinosinusitis
- Vocal cord dysfunction
- Dysfunctional breathing
- Reflux
- BMI 35 kg/m^2

Borderline sensitisation to rye grass pollen and dust mites

EOS 0.52 × 10^9/L
FeNO 47 ppb

ACQ, Asthma Control Questionnaire; **BMI,** body mass index; **EOS,** eosinophil count; **FeNO,** fractional exhaled nitric oxide; **FEV_1,** forced expiratory volume in 1 second

Initial management in 2016/17

Panel discussion

Severe adult-onset eosinophilic asthma with CRS and multiple comorbidities

- Asthma education
- Proton pump inhibitor
- Intranasal steroids
- Speech therapy
- Dietitian review

Mepolizumab commenced early 2017 when available on PBS

CRS, chronic rhinosinusitis; **PBS**, Pharmaceutical Benefits Scheme

Initial response to mepolizumab in 2017

- ACQ score 0.6
- No exacerbations
- FEV_1 2.09 (87% predicted) with no reversibility

ACQ, Asthma Control Questionnaire; **FEV_1,** forced expiratory volume in 1 second

Ongoing response to mepolizumab in 2020

- ***2 exacerbations*** over 12 months
- No interval symptoms
- ACQ score 0.6, FEV_1 2.38 (103% predicted) with no reversibility

ACQ, Asthma Control Questionnaire; **FEV_1,** forced expiratory volume in 1 second

Ongoing response to mepolizumab in 2020

- ***2 exacerbations*** over 12 months
- No interval symptoms
- ACQ score 0.6, FEV_1 2.38 (103% predicted) with no reversibility

Re-escalated budesonide–formoterol puffer to 4 puffs BD, tiotropium and montelukast

No further exacerbations for 24 months

ACQ, Asthma Control Questionnaire; **BD,** twice daily; **FEV_1,** forced expiratory volume in 1 second

Subsequent deterioration in 2022

- ***2 exacerbations*** over 12 months
- **ACQ score 2.2** with ongoing interval symptoms
- **FEV_1 1.76** (75% predicted) with 12% reversibility
- Reflux symptoms
- (Low Nijmegen and VCD-Q scores)
- Eosinophils 0.09×10^9/L

Management

- Asthma education review
- Dietitian referral
- Proton pump inhibitor restarted
- Intranasal steroid restarted

ACQ, Asthma Control Questionnaire; **FEV_1,** forced expiratory volume in 1 second; **VCD-Q,** Vocal Cord Dysfunction Questionnaire

Subsequent deterioration and management switch in 2022

- ***2 exacerbations*** over 12 months
- **ACQ score 2.2** with ongoing interval symptoms
- **FEV_1 1.76** (75% predicted) with 12% reversibility
- Reflux symptoms
- (Low Nijmegen and VCD-Q scores)
- Eosinophils 0.09 × 10^9/L

Management

- Asthma education review
- Dietitian referral
- Proton pump inhibitor restarted
- Intranasal steroid restarted

Biologic switch from mepolizumab to dupilumab

ACQ, Asthma Control Questionnaire; **FEV_1,** forced expiratory volume in 1 second; **VCD-Q,** Vocal Cord Dysfunction Questionnaire

2023 response to dupilumab

- ACQ score 0.6
- FEV_1 2.29 (104% predicted) with no reversibility
- No exacerbations over 7 months (despite COVID infection)

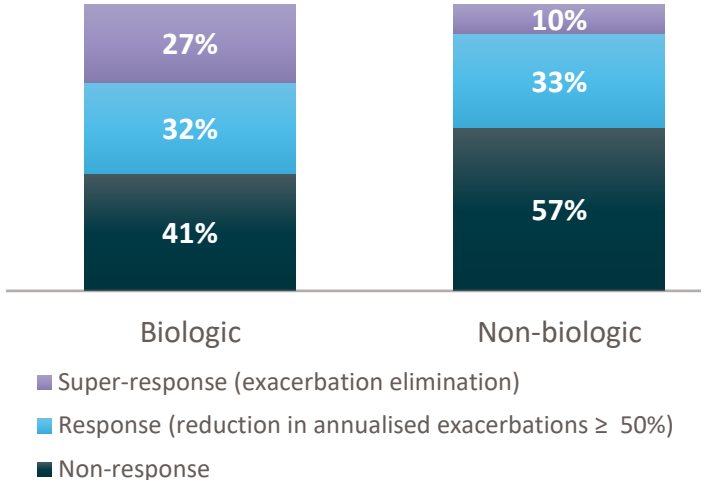
ACQ, Asthma Control Questionnaire; **COVID,** coronavirus disease; **FEV_1,** forced expiratory volume in 1 second

Discussion points

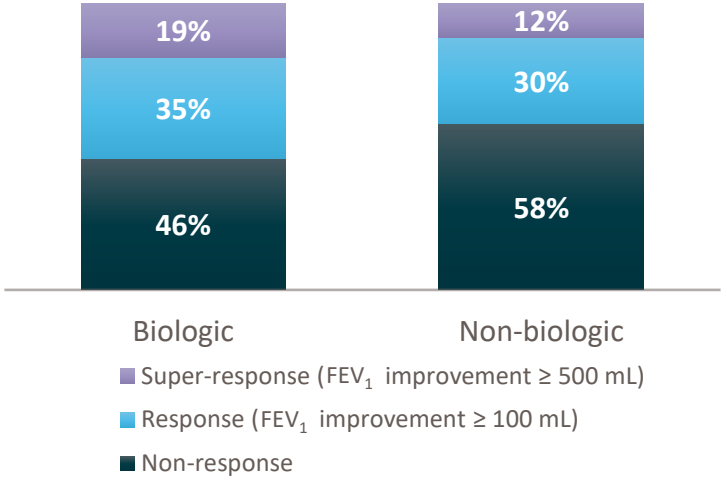
1. Fluctuating asthma control over time
2. Multiple asthma domains to consider – not just exacerbations or symptom control
3. Inhaler back-titration confounding response assessments
4. Comorbidity contributions
5. Patient behaviour and medication use
6. Possibility of disease progression
7. Limitations to biologic effectiveness
8. Limited data on switching biologics

Biologic effectiveness following biologic initiation in severe asthma—International Severe Asthma Registry findings (n = 8,451)

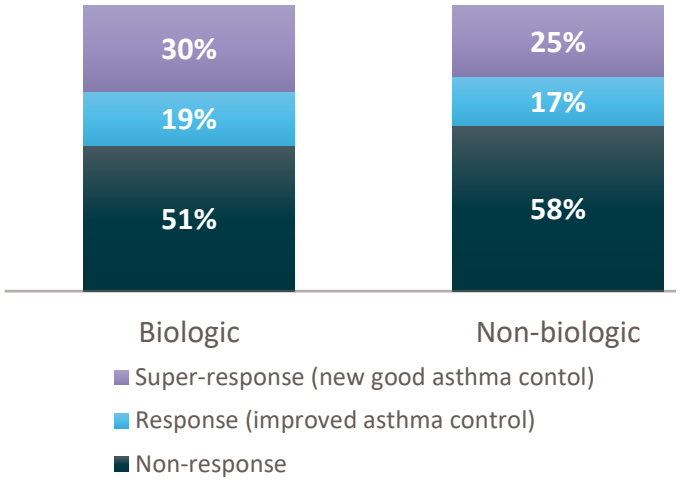
Annualised exacerbations



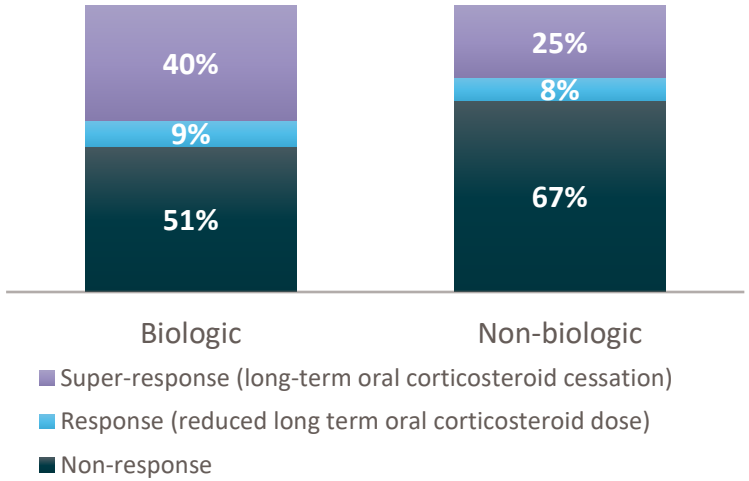
FEV_1 improvement



Asthma control



Oral corticosteroid

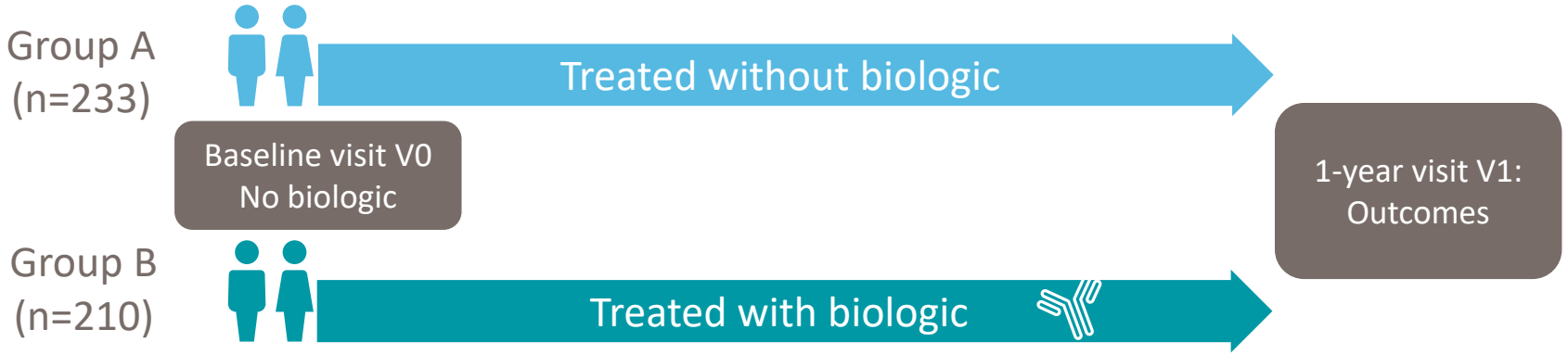


- ✓ **Biologic patients 'do better'** (i.e., more responders/super responders among patients who initiated biologics than not [P < 0.001 for all outcomes], although some non-biologic patients 'do well too')
- **Response differs between different domains**
- **Response to biologics is incomplete**

FEV_1, forced expiratory volume in 1 second

Denton E, et al. Am J Respir Crit Care Med. 2023;207:A4753.

Biologic effectiveness following biologic initiation in severe asthma—German Asthma Net Severe Asthma Registry findings



‘Good’ response		Clinical remission	
No exacerbations or reduced ≥ 75%, no OCS or reduced ≥ 75%, ACT score improved ≥ 3 and score ≥ 20, or ACT score improved ≥ 6		No exacerbation, no daily OCS, ACT score ≥ 20	
Biologic	**No biologic**	**Biologic**	**No biologic**
61.4%	34.8%	**37.6%**	17.2%

Biologic response is incomplete

ACT, Asthma Control Test; **OCS**, oral corticosteroids

Milger K, et al. J Allergy Clin Immunol Pract. 2023;S2213-2198(23)00646-3.

Discussion points

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RESOURCES

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ADVANCES IN TYPE 2 INFLAMMATORY DISEASES

Download the slides and your certificate of attendance

Remission or ‘super responders’ in severe asthma: what should we target and when should we switch?

Full reference list

This meeting will be available online in the coming weeks

View the recent ADVENT interactive clinical tutorials and find out about future events on Sanofi Campus

Sanofi Campus is built exclusively for Healthcare Professionals, featuring the latest news, education, and patient support materials.

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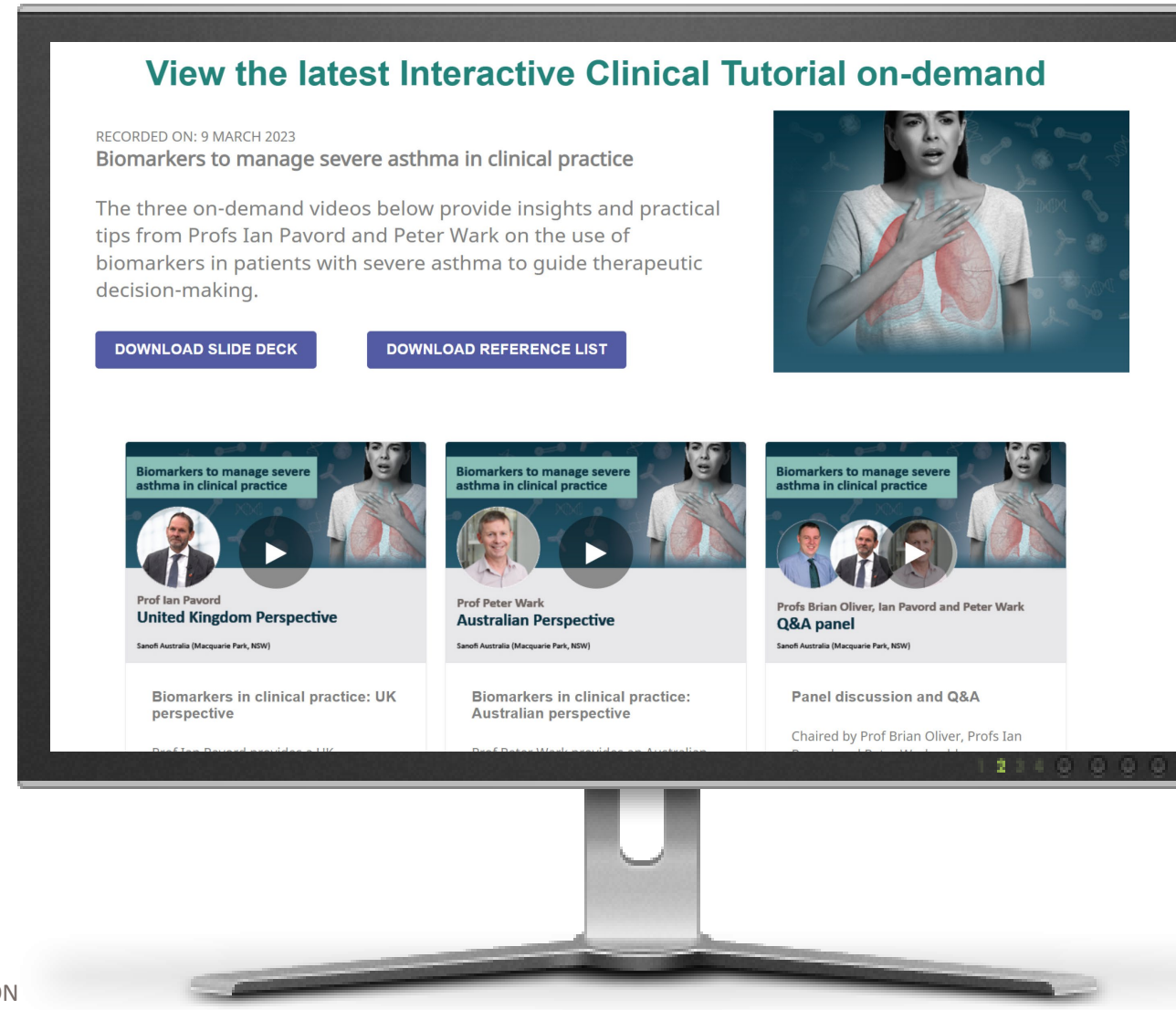

Previous Respiratory clinical tutorials available on demand

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Registration is required to view content.

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- Watch the ADVENT respiratory series from 2020-2022
- Access medical education resources for Type 2 inflammatory diseases developed and endorsed by Australian and international experts

Prescribing Information

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Thank you

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