Research Review™
PRODUCT REVIEW

Baricitinib (Olumiant®) in moderate-to-severe active rheumatoid arthritis

Making Education Easy 2018

Independent commentary by Associate Professor Andrew Östör

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Abbreviations used in this issue:

ACR20/50/70 = 20%/50%/70% improvement according to American College of Rheumatology criteria; **bDMARDs** = biologic disease-modifying antirheumatic drugs; **CYPP3A4** = cytochrome P450 3A4; **cDMARDs** = conventional disease-modifying antirheumatic drugs; **CDAI** = Clinical Disease Activity Index; **DAS28-CRP** = 28-joint Disease Activity Score, based on the level of high-sensitivity C-reactive protein; **GFR** = glomerular filtration rate; **HAQ-DI** = Health Assessment Questionnaire–Disability Index; **IL** = interleukin; **IFN** = interferon; **JAK** = Janus kinase; **NMSC** = nonmelanoma skin cancer; **RA** = rheumatoid arthritis; **SDAI** = Simplified Disease Activity Index; **STATs** = signal transducers and activators of transcription; **TNF** = tumor necrosis factor; **TYK** = tyrosine kinase.

This review summarises important pharmacological and clinical characteristics of the orally-administered, small-molecule, JAK inhibitor baricitinib (Olumiant®) in patients with rheumatoid arthritis (RA). Baricitinib has been approved in Australia for the treatment of moderate-to-severe active RA in adult patients who have responded inadequately, or who are intolerant, to one or more disease modifying anti-rheumatic drugs (DMARDs).[1] In the 52-week RA-BEAM study in patients with RA who had an inadequate response to methotrexate, baricitinib was associated with significant clinical improvements compared with placebo and adalimumab. Baricitinib may be administered orally as monotherapy or in combination with conventional DMARDs.

Introduction

Rheumatoid arthritis (RA) is a chronic systematic, autoimmune inflammatory disease, characterised by progressive destruction of synovial joints.[2-7] Symptoms associated with RA include pain, morning stiffness, joint swelling and tenderness, loss of movement and fatigue.

RA is diagnosed on the basis of four criteria: number and pattern of joints involved, disease duration greater than 6 weeks, raised inflammatory markers (such as erythrocyte sedimentation rate or C-reactive protein [CRP] level) and positive serology (e.g. the rheumatoid factor or cyclic citrullinated peptide antibody).[2]

The prevalence of RA varies according to the population studied, statistical methods and disease definitions. Nevertheless, the Global Burden of Disease 2010 study estimated the global prevalence of RA to be 0.24%.[8] The prevalence of RA in Australia is estimated to be 0.6%.[9] RA more typically occurs in women.[3, 8, 10] RA affects Australians of all ages, with 58% of those affected by this disease aged 25 to 64 years.[6]

RA leads to severe disability, and people with this disease are more likely to have anxiety, depression and low self-esteem.[11] RA is also associated with increased mortality due to related complications and comorbidities such as infections and cardiovascular disease.[12]

RA impacts a patient's health-related quality of life, with patients reporting impaired physical functioning, work productivity and activities of daily living.[13-15] Consequently, RA places considerable economic burden on both the individual and society (**Figure 1**).[13, 16, 17] RA cost the Australian health system over $AU550 million in 2015, and this cost is projected to increase to over $AU755 million by 2030 unless the condition can be better prevented and/or managed.[17]

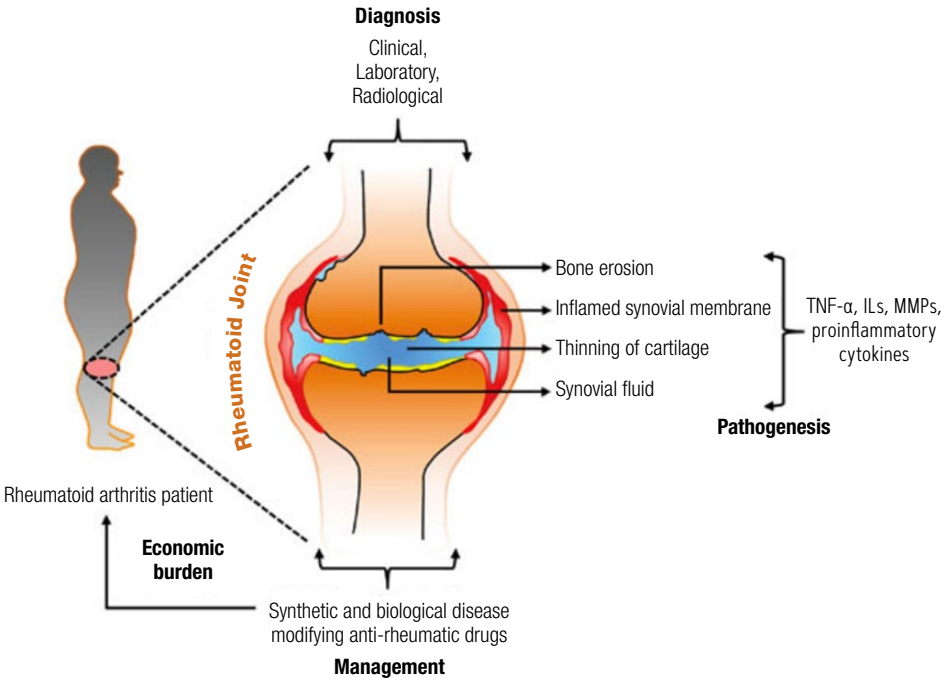

Figure 1. Impact of rheumatoid arthritis.

Source: Graphical abstract: Fazal SA, et al. Endocr Metab Immune Disord Drug Targets. 2018;18(2):98-109.

ILs = interleukins; MMPs = matrix metalloproteinase; TNF = tumour necrosis factor.

A specific cause for RA has not been identified, but both genetic and environmental factors have been implicated.[18, 19] Various immune modulators and signaling pathways are involved in the pathogenesis of RA. T cells and B cells are implicated, along with pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1 and IL-17. The pro-inflammatory cytokines implicated in the pathogenesis of RA, signal through activation of intracellular tyrosine kinases (TYK), including Janus kinases (JAKs).[20] JAKs transmit signals from cytokines bound to receptors on the cell surface to signal transducers and activators of transcription (STATs: **Figure 2**).[21, 22]

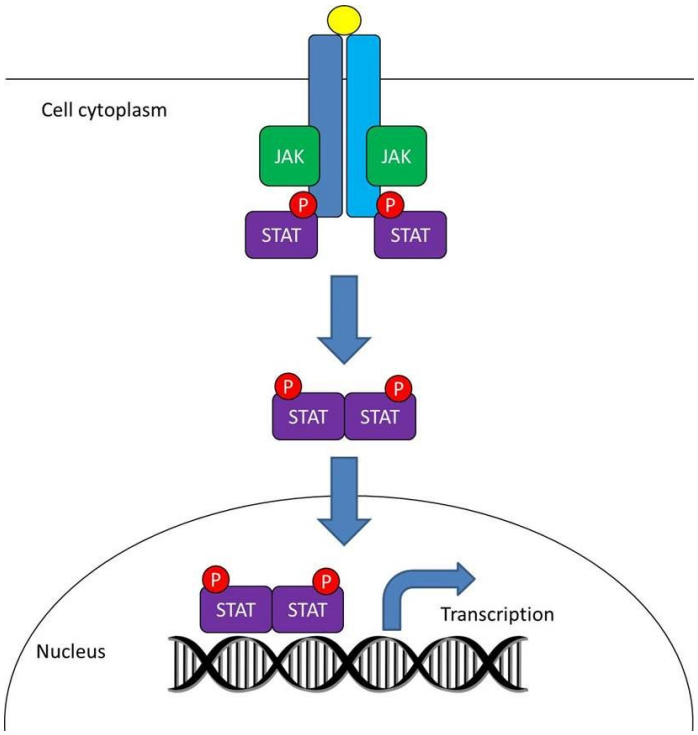

Figure 2. Binding of cytokines (yellow) to their receptors on the cell surface results in JAK activation and subsequent cross-phosphorylation of the receptors. Signal transducers and activators of transcription (STATs) then attach to the phosphorylated receptors, dimerize, and translocate to the nucleus where they drive the expression of proteins involved in inflammatory processes such as rheumatoid arthritis.

Source: Adapted from Ivashkiv LB, et al. Arthritis Res Ther. 2004;6(4):159-168.

Rheumatoid arthritis treatment

There is no cure for RA. However, an increased understanding of the pathogenic mechanisms involved in RA in the past 20 years has led to the development of treatment strategies that have resulted in major improvements in patient outcomes.[6] Much of this success has been the shift in the treatment paradigm to early treatment with conventional disease-modifying antirheumatic drugs (cDMARDs) such as methotrexate.[6] Nevertheless, many patients continue to have active disease despite treatment with cDMARDs or do not tolerate cDMARD therapy. In this situation, a biologic disease-modifying anti-rheumatic drug (bDMARD), typically a tumour necrosis factor inhibitor, is prescribed.[6] Biologic DMARDs became available in Australia in 2003, broadening the treatment options for patients with RA.[2, 5-7, 23] Biologic DMARDs inhibit circulating or membrane-bound cytokines (e.g. TNF-α and IL-6) or cellular targets (e.g. B and T cells). Examples include the TNF inhibitors (e.g. adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the IL-6 inhibitor (tocilizumab), and agents that target T cells (e.g. abatacept) or B cells (e.g. rituximab). In Australia, cDMARDs can be prescribed by general practitioners, but only rheumatologists or clinical immunologists can prescribe bDMARDs.[6]

JAK inhibitors have emerged as a new class of targeted, synthetic, small molecules that can be used to treat RA.[21] Tofacitinib was the first JAK inhibitor approved for the treatment of RA in Australia,[24] with the approval of baricitinib, a selective JAK1/JAK2 inhibitor, occurring earlier this year.[1]

Baricitinib

Baricitinib (Olumiant®) is an orally-administered selective JAK1/JAK2 inhibitor. In February 2017, baricitinib was approved in the EU, as monotherapy or in combination with methotrexate, for the treatment of moderate-to-severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs.[25] On the 23 January 2018, baricitinib was registered by the Australian Therapeutic Goods Administration for the treatment of moderate-to-severe active RA in adult patients who have responded inadequately, or who are intolerant, to one or more DMARDs.[1]

Baricitinib should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of RA.[1] As with biologics, patients should also be screened for viral infections (e.g. hepatitis B and C and human immunodeficiency virus), and tuberculosis (TB), before initiating treatment with baricitinib.

Please refer to the full Product Information before prescribing.[1]

Dosage and administration

Baricitinib is administered orally, at a recommended dosage of 4 mg once daily.[1] Baricitinib may be administered as monotherapy or in combination with cDMARDs.

In patients with an inadequate response to cDMARDs who have moderate disease severity, limited risk of progressive joint damage and moderate impairment of physical function, a dose of 2 mg once daily may be appropriate.[1] Baricitinib 2 mg once daily may also be appropriate for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering.[1]

Baricitinib can be administered with or without food.[1]

Patients with renal impairment

In patients with moderate, stage 3 renal impairment (estimated glomerular filtration rate [GFR] 30 to ≤60 mL/min/1.73 m^2), the recommended dose of baricitinib is 2 mg once daily.[1]

Baricitinib is not recommended for use in patients with severe and end stage renal impairment stage 4 and 5 (estimated GFR of <30 mL/min/1.73 m^2).

Contraindications

Patients with known hypersensitivity to baricitinib or any of the excipients in the product.[1]

Baricitinib must not be used in combination with bDMARDs.[1]

Precautions

Infections

Baricitinib therapy is associated with an increased rate of infections (e.g. upper respiratory tract infections).[1] Caution is needed if baricitinib is used in patients with clinically important chronic, active, or recurrent infection. If a patient develops a serious infection, baricitinib should be interrupted until the infection is controlled.

Tuberculosis

Patients should be screened for TB before initiating baricitinib therapy and should not be administered to patients with active TB. Anti-TB therapy should be considered prior to baricitinib initiation in patients with previously untreated latent TB.[1]

Viral reactivation

In clinical studies involving baricitinib, cases of viral reactivation (e.g. herpes zoster reactivation) were reported.[1] If a patient develops herpes zoster, baricitinib should be interrupted until the episode resolves. Patients should be screened for viral hepatitis before starting baricitinib therapy.

Venous thromboembolism

Deep venous thrombosis (DVT) and pulmonary embolism (PE) events have been reported in patients receiving baricitinib. Baricitinib should be used with caution in patients with risk factors for deep vein thrombosis or pulmonary embolism such as older age, obesity or a medical history of DVT/PE. Caution is also advised in patients undergoing surgery and immobilization.[1]

Malignancy

The risk of malignancy, including lymphoma, is increased in patients with RA. Immunomodulatory medicinal products, such as baricitinib may increase the risk of malignancy.[1] In the placebo-controlled phase 2/3 clinical studies in rheumatoid arthritis patients, two malignancies (excluding nonmelanoma skin cancer [NMSC]) were diagnosed in two patients treated with baricitinib 4 mg, compared to two malignancies (excluding NMSC) in patients in the placebo group. There were no cases of lymphoma reported during the placebo-controlled studies.[1]

Pharmacological Properties

Mechanism of action

Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2.[1] Baricitinib inhibited the activities of JAK1, JAK2, TYK2 and JAK3 in isolated enzyme assays, with IC_{50} (the concentration of a drug required for 50% inhibition) values of 5.9, 5.7, 53 and >400 nM, respectively.[1, 26] As a result, the generation of cytokines such as IL-2, -6, -12, -23, as well as granulocyte-macrophage colony stimulating factor and interferon (IFN)-γ, is inhibited.[1, 26, 27]

Pharmacokinetics

Baricitinib is rapidly absorbed with a median time to maximum plasma concentration of approximately 1 hour and an absolute bioavailability of approximately 80% following oral administration.[1, 28] Food does not influence the drug's pharmacokinetics.

Baricitinib distributes into tissues, with a mean volume of distribution following intravenous infusion administration of 76 L.[1] Approximately 50% of circulating baricitinib is bound to plasma proteins.[1]

Approximately 6% of the baricitinib dose is metabolised to four oxidation products by cytochrome P450 3A4 (CYP3A4); the rest remains unchanged.[1] Baricitinib is eliminated in the urine (75% of the administered dose) or the faeces (20% of the administered dose).

The mean half-life of baricitinib in patients with RA is 12.5 hours.[1]

Drug interactions

In vitro, baricitinib did not significantly inhibit or induce the activity of cytochrome P450 enzymes, and it had no clinically meaningful effect on CYP3A substrates.[1] In clinical studies, co-administration of baricitinib with the CYP3A substrates simvastatin, ethinyl estradiol, or levonorgestrel did not result in any meaningful changes to these drugs. Although baricitinib inhibits a number of transporter proteins *in vitro,* clinically relevant drug interactions via this mechanism are considered unlikely.[1] In clinical studies, there were no clinically meaningful effects when baricitinib was coadministered with digoxin (a P-glycoprotein substrate) or methotrexate (substrate of several transporters).

Clinical trial evidence for baricitinib

The approval of baricitinib was based on efficacy and safety data obtained from four randomised, double-blind, multicentre studies in patients with active RA. A brief summary of these trials is provided in table 1.[1, 29-32] Patients from these trials entered a long-term extension trial (RA-BEYOND).

The primary outcome in these randomised controlled trials was the proportion of people achieving a 20% improvement in the American College of Rheumatology response criteria (ACR20) at week 12 or 24 (**Table 1**).

This review will focus on data from the 52-week RA-BEAM trial.[1, 30]

RA-Beam Trial

Study design and baseline characteristics

RA-BEAM was a randomised, double-blind, placebo- and active-controlled, parallel-group 52-week study that was conducted in 281 centres in 26 countries.[1, 30] The patients had active RA, and were randomly assigned to placebo, baricitinib 4 mg once daily, or 40 mg of adalimumab every other week. Nearly all patients (>99%) were also receiving background therapy with methotrexate; the majority had previously received at least two conventional synthetic DMARDs. A total of 1305 patients were treated and qualified for analysis.

Table 1: Phase 3 trials involving baricitinib in patients with active RA

	Patient population	Concomitant DMARDs	Treatment	ACR20 (% patients)
RA-BEGIN (52 weeks)[1, 29] (n=584)	Active RA, DMARD-naive (≤3 doses of MTX allowed)[a]	Required: MTX (if assigned) Allowed: NSAIDs, prednisone <10 mg daily	Baricitinib 4 mg/day	77+
			Baricitinib 4 mg/day + MTX	78
			MTX	62
				(24 weeks)
RA-BEAM (52 weeks)[1, 30] (n=1305)	Active RA on stable background MTX (prior bDMARDs not allowed)	Required: MTX Allowed: NSAIDs, prednisone <10 mg daily	Placebo	40
			Baricitinib 4 mg/day	70*†
			Adalimumab 40 mg biweekly	61
				(12 weeks)
RA-BUILD[1, 31] (24 weeks) (n=684)	Active RA refractory to cDMARDs (prior bDMARDs not allowed)	Allowed: up to 2 cDMARDs without MTX, NSAIDs, prednisone ≤10 mg daily	Placebo	39
			Baricitinib 2 mg/day	66*
			Baricitinib 4 mg/day	62*
				(24 weeks)
RA-BEACON[1, 32] (24 weeks) (n=527)	Active RA refractory to bDMARDs (TNF-α inhibitors)	Allowed: cDMARDs, NSAIDs, prednisone ≤10 mg daily	Placebo	27
			Baricitinib 2 mg/day	49*
			Baricitinib 4 mg/day	55*
				(12 weeks)

[a]Baricitinib is not indicated for this patient population in Australia. bDMARDs = biological disease-modifying antirheumatic drugs; cDMARDs = conventional disease-modifying antirheumatic drugs; MTX = methotrexate; NSAIDs = non-steroidal anti-inflammatory drugs; TNF = tumour necrosis factor.

*p ≤ 0.001 vs placebo; +p ≤ 0.01 vs MTX monotherapy; †p < 0.05 vs adalimumab.

Further details of the study design are given in **Figure 3**.

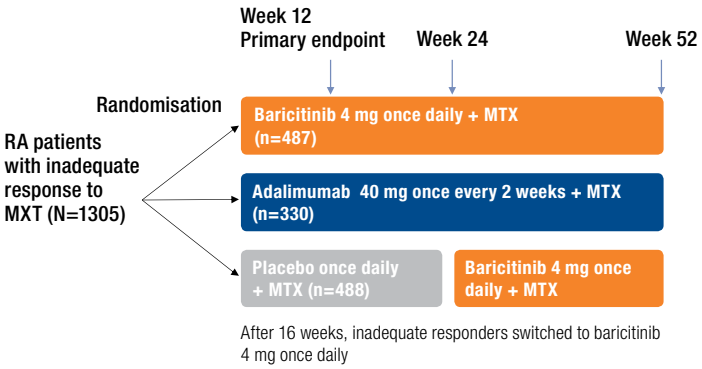

Figure 3. Trial design of RA-BEAM

ACR20 = American College of Rheumatology ≥ 20% improvement criteria; BARI = baricitinib; MTX = methotrexate; OD = once daily; PBO = placebo.

Patients

Patients were aged ≥18 years and had active RA (≥six tender joints of 68 examined, ≥six swollen joints of 66 examined, and a high-sensitivity serum C-reactive protein level of ≥6 mg/L).[1, 30] This study included patients whose disease responded inadequately to methotrexate, but patients who had received previous biologic DMARD therapy were excluded.

As might be expected for RA patients with an inadequate response to methotrexate, the duration of disease was long (mean 10 years).[1, 30] Patients had a mean disease activity score in 28 joints calculated with C-reactive protein (DAS28-CRP) scores of 5.7 to 5.8.

Efficacy

At week 12, baricitinib 4 mg once daily was associated with significantly higher ACR20 (primary endpoint) or ACR50/70 response rates than placebo or adalimumab (**Table 2**).[1, 30]

Table 2. ACR response rates[1]

Patients (%)	Baricitinib 4 mg once daily plus methotrexate (n=487)	Adalimumab 40 mg every other week plus methotrexate (n=330)	Placebo plus methotrexate (n=488)
ACR20			
Week 12	70*†	61*	40
Week 24	74*†	66*	37
Week 52	71††	62	NA
ACR50			
Week 12	45*††	35*	17
Week 24	51*	45*	19
Week 52	56†	47	NA
ACR70			
Week 12	19*†	13*	5
Week 24	30*†	22*	8
Week 52	37	31	NA

ACR 20/50/70 = 20%/50%/70% improvement according to American College of Rheumatology criteria; NA = not applicable. *p ≤ 0.001 vs placebo; †p ≤ 0.05, ††p ≤ 0.01 vs adalimumab.

The time to onset of efficacy (ACR 20/50/70 response) was rapid, with responses being significantly greater than placebo as early as week 1 (**Figure 4**). Continued, durable response rates were observed, with ACR20/50/70 responses maintained for up to 52 weeks (**Table 2 and Figure 4**).

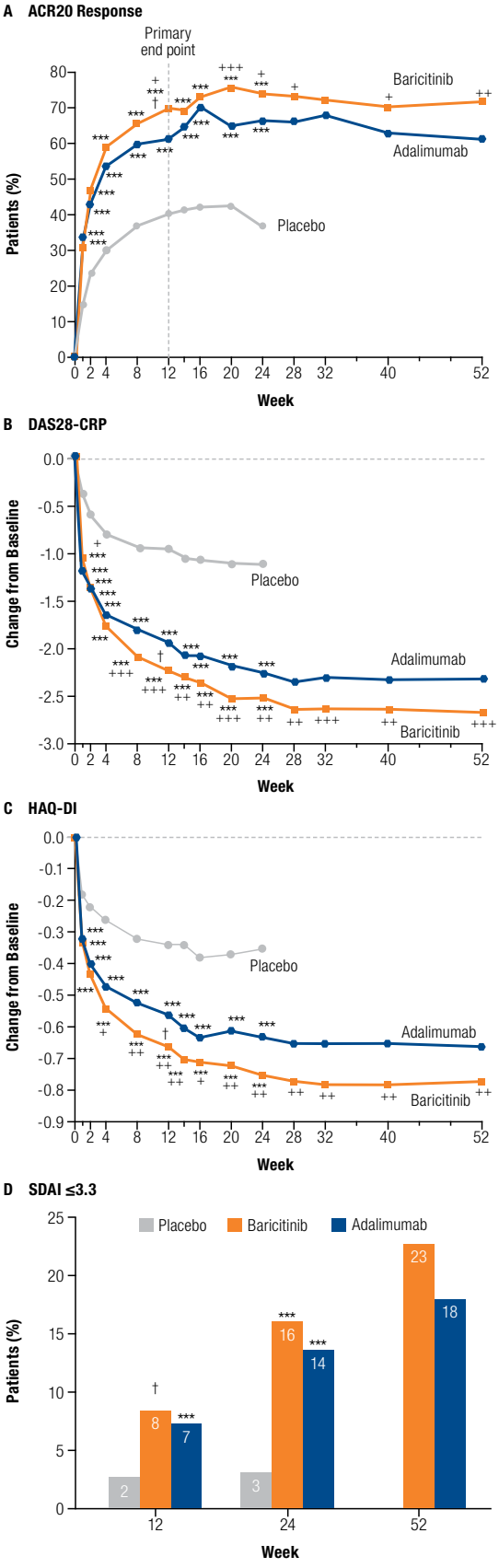

Figure 4. Efficacy endpoints in RA-BEAM.[1,30]

Source: Taylor PC, et al. N Engl J Med. 2017;376(7):652-662.

ACR20 ≥ 20% improvement in American College of Rheumatology criteria; DAS28-CRP = 28-joint Disease Activity Score, based on the level of high-sensitivity C-reactive protein; HAQ-DI = Health Assessment Questionnaire–Disability Index; SDAI = Simplified Disease Activity Index.*p ≤0.05, **p ≤0.01, ***p ≤0.001 vs placebo; +p ≤0.05, ++p ≤0.01, +++p ≤0.001 vs adalimumab; †p ≤0.05 vs placebo or adalimumab.

Baricitinib was also associated with significant improvements compared with placebo for other secondary and exploratory endpoints, including Health Assessment Questionnaire [HAQ] score (**Figure 4**), DAS28-CRP (**Figure 4**), remission according to the simple disease activity index (SDAI; **Figure 4**), Clinical Disease Activity Index (CDAI) and the individual components of the ACR response rate.[1, 30]

Both baricitinib and adalimumab were associated with significant reductions in the radiographic progression of structural joint damage, compared with placebo, at week 24 and week 52.[1, 30]

Safety outcomes

Adverse events were more frequent with baricitinib (71% of patients) and adalimumab (68%) than with placebo (60%) in the first 24 weeks, but rates of adverse events (including infections) with baricitinib and adalimumab were similar over the 52 weeks of treatment.[1, 30] Serious adverse events were reported in 5% of patients treated with placebo, 5% with baricitinib and 2% with adalimumab in the first 24 weeks. Rates of serious infection were similar with placebo, baricitinib, and adalimumab in the first 24 weeks (1%, 1% and <1%, respectively) and with baricitinib and adalimumab in the first year (2% each).

Reductions in neutrophil counts, increases in alanine aminotransferase and creatinine levels, and increases in low-density and high-density lipoprotein cholesterol levels were associated with baricitinib and adalimumab.

At 52 weeks, three patients in the baricitinib group and two in the adalimumab group discontinued treatment because of liver abnormalities.[1, 30]

Safety analysis of baricitinib in clinical trials

Analysis of data from phase II and III clinical trials of up to 16 weeks duration indicated that baricitinib is generally well tolerated, with commonly reported adverse reactions including upper respiratory tract infection, herpes simplex and herpes zoster infection, nausea, increased LDL cholesterol levels, increased alanine transferase levels and thrombocytosis.[1]

Analysis of data from an ongoing extension study involving 3492 patients with active rheumatoid arthritis who had received baricitinib for 6637 total patient-years (PY) of exposure indicated that baricitinib was generally well tolerated with up to 5.5 years of exposure.[33] No differences occurred between baricitinib 4 mg compared with placebo in the number of adverse events that resulted in permanent study drug discontinuation, death, malignancy, serious infection or major adverse cardiovascular event. The incidence rate per 100 PY for herpes zoster infection was significantly higher in patients treated with baricitinib 4 mg than placebo (4.3 vs 1.0; $p < 0.05$). Malignancy (excluding non-melanoma skin cancer) incidence rates were 1.3 in those treated with baricitinib 4 mg (as-treated analysis). Across all baricitinib recipients (all dosages), the incidence rate per 100 PY for lymphoma was 0.09, for gastrointestinal perforation was 0.05, and for tuberculosis was 0.15. Less than 1% of patients discontinued due to abnormal laboratory results.

Expert commentary on RA-BEAM

RA-BEAM forms the pinnacle of the extensive clinical trial programme using baricitinib in patients with active RA. The remarkable feature of the RA-BEAM study was the demonstration of superiority of baricitinib over adalimumab for the ACR20 response at week 12 (the primary outcome measure) in patients with an insufficient response to methotrexate, who continued on background methotrexate. Furthermore, baricitinib displayed statistically significant benefit over adalimumab in multiple secondary endpoints including clinical and patient reported outcomes. This has not been seen previously in trials involving RA patients and thus the results set a new benchmark in the management of RA. In addition, the safety profile is consistent with what is expected of such disease modifying agents and no new flags have been raised. RA-BEAM is a landmark study and will help to herald a new era in the management of inflammatory arthritis.

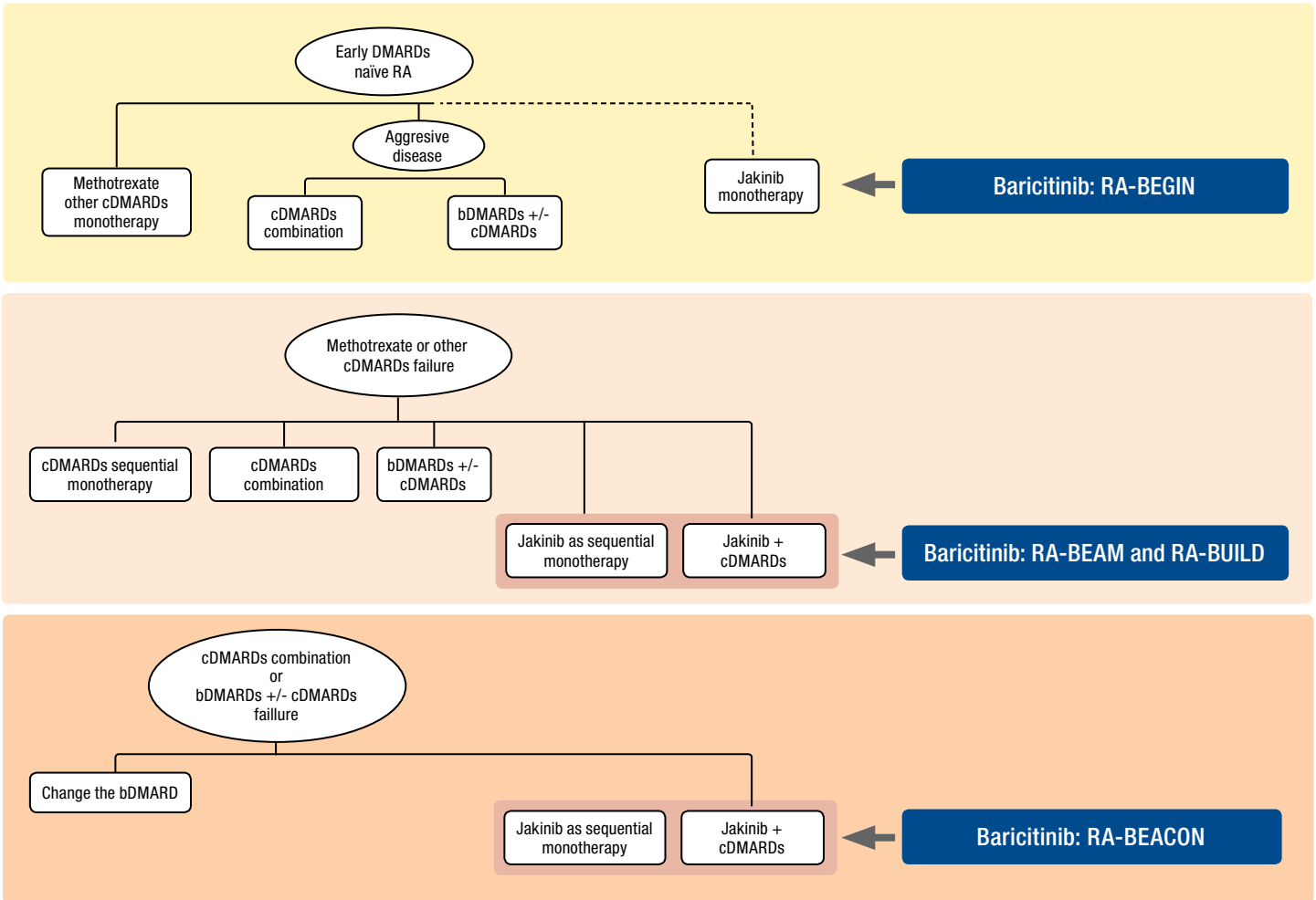

Figure 5. Scenarios for the use of baricitinib in patients with RA.
Source: Adapted from Semerano L, et al. Expert Opin Investig Drugs. 2016;25(12):1355-1359. bDMARDs = biological disease-modifying antirheumatic drugs; cDMARDs = conventional disease-modifying antirheumatic drugs; Jakinib = Janus kinase inhibitor

Place of baricitinib in RA therapy

Baricitinib is currently approved in Europe and Australia for the treatment of moderate-to-severe active RA among adult patients with an inadequate response or intolerance to at least one DMARD.[1, 25] Data from RA-BEAM[1, 30] support its use as add-on therapy to those who have failed methotrexate therapy or previous cDMARDs (**Figure 5**). Data from RA-BUILD demonstrated that treatment effects compared to placebo were robust whether baricitinib was used as monotherapy, in combination with methotrexate, or in combination with cDMARDs other than methotrexate.[1]

Data from another phase 3 baricitinib trial (RA-BEACON[1, 32]) indicate that baricitinib was effective in patients who were insufficient responders to bDMARDs +/- cDMARDs.

Data from the 52-week RA-BEGIN trial demonstrated that baricitinib was superior to MTX in patients with early cDMARDs naïve RA.[1, 29] However, baricitinib is not currently approved for these patients in Australia. Moreover, given the well-established place of methotrexate in the early treatment of RA it is unlikely that baricitinib will replace methotrexate as first-line intervention.[34] Conversely, as clinical experience with baricitinib increases it is possible that early intervention with baricitinib may occur in patients with severe disease.[34]

Commentary on place of baricitinib in RA treatment

Baricitinib forms part of the new wave of management options for RA. Rheumatologists and patients have benefited greatly from the introduction of biologic agents for the treatment of inflammatory arthritis. However, one of the major drawbacks is the requirement for parenteral administration. Baricitinib, a once daily, oral therapy has shown benefit in multiple RA populations including those who have failed on methotrexate, cDMARDs and anti-TNF as well as in methotrexate-naive groups. In addition, evidence exists for its effective use as a mono-therapeutic agent which is critical for the large proportion of patients who are unable to tolerate methotrexate. It is important to note that no major safety issues have been raised, although longer term data will be required to clarify the true spectrum of untoward effects. With its superiority over adalimumab in RA-BEAM, baricitinib is a rising star in the management of RA.

Conclusion

The orally administered JAK inhibitor baricitinib represents an important addition to the treatment of moderate-to-severe RA. The RA-BEAM study demonstrated that baricitinib was effective as add-on therapy in patients who were insufficient responders to methotrexate. In this trial, baricitinib induced higher rates of clinical response than adalimumab, with a similar tolerability profile.

Conclusion from expert

The management of inflammatory arthritis including RA has undergone a transformation over the last two decades. Biologic DMARDs opened a new world of therapeutics and outcomes for patients with autoimmune disease leading to hitherto unprecedented outcomes. We now appear to be rapidly entering another age in the treatment of such conditions with the introduction of targeted, synthetic DMARDs into routine clinical practice. A number of benefits exist for this group of agents including speed of onset, durability of response, safety record and most critically oral administration. As far as patient convenience is concerned, this is highly prized which is reflected in the fact that Australia has the fastest uptake of targeted, synthetic DMARDs in the world. Baricitinib with its once-daily dosing and evidence for superiority over adalimumab (as seen in the RA-BEAM) study, will no doubt improve the lives of patients with RA and consolidate the new era in the management of autoimmune disease.

References

1. Eli Lilly Australia Pty Limited. Baricitinib (Olumiant®): Australian prescribing information. 2018. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01225-1&d=20180427161146224 83
2. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-2581.
3. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376(9746):1094-1108.
4. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205-2219.
5. Singh JA, Saag KG, Bridges SL, Jr., et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.
6. Arthritis Australia. 2014. Time to move: rheumatoid arthritis - a national strategy to reduce a costly burden. Available at: http://www.arthritisaustralia.com.au/.
7. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960-977.
8. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316-1322.
9. Harrison C, Henderson J, Miller G, et al. The prevalence of diagnosed chronic conditions and multimorbidity in Australia: A method for estimating population prevalence from general practice patient encounter data. PLoS One. 2017;12(3):e0172935.
10. Ahlmen M, Svensson B, Albertsson K, et al. Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. Ann Rheum Dis. 2010;69(1):230-233.
11. Covic T, Cumming SR, Pallant JF, et al. Depression and anxiety in patients with rheumatoid arthritis: prevalence rates based on a comparison of the Depression, Anxiety and Stress Scale (DASS) and the hospital, Anxiety and Depression Scale (HADS). BMC Psychiatry. 2012;12:6.
12. Lassere MN, Rappo J, Portek IJ, et al. How many life years are lost in patients with rheumatoid arthritis? Secular cause-specific and all-cause mortality in rheumatoid arthritis, and their predictors in a long-term Australian cohort study. Intern Med J. 2013;43(1):66-72.
13. Taylor PC, Moore A, Vasilescu R, et al. A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. Rheumatol Int. 2016;36(5):685-695.
14. Hunter DJ, Riordan EA. The impact of arthritis on pain and quality of life: an Australian survey. Int J Rheum Dis. 2014;17(2):149-155.
15. Staples MP, March L, Lassere M, et al. Health-related quality of life and continuation rate on first-line anti-tumour necrosis factor therapy among rheumatoid arthritis patients from the Australian Rheumatology Association Database. Rheumatology (Oxford). 2011;50(1):166-175.
16. Fazal SA, Khan M, Nishi SE, et al. A clinical update and global economic burden of rheumatoid arthritis. Endocr Metab Immune Disord Drug Targets. 2018;18(2):98-109.
17. Arthritis Australia. Counting the cost: the current and future burden of arthritis 2016.
18. Tobon GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. J Autoimmun. 2010;35(1):10-14.
19. Frisell T, Saevarsdottir S, Askling J. Family history of rheumatoid arthritis: an old concept with new developments. Nat Rev Rheumatol. 2016;12(6):335-343.
20. Banerjee S, Biehl A, Gadina M, et al. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. Drugs. 2017;77(5):521-546.
21. O'Shea JJ, Plenge R. JAK and STAT signaling molecules in immunoregulation and immune-mediated disease. Immunity. 2012;36(4):542-550.
22. Ivashkiv LB, Hu X. Signaling by STATs. Arthritis Res Ther. 2004;6(4):159-168.
23. Australian Government: Australasian Institute of Health and Welfare. The use of disease-modifying anti-rheumatic drugs for the management of rheumatoid arthritis. 2011.
24. Pfizer Australia Pty Ltd. Tofacitinib (as citrate) tablet (XELJANZ®): Australian prescribing information. 2015.
25. European Medicines Agency. 2017. Baricitinib (Olumiant®): summary of product characteristics. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004085/human_med_002074.jsp.
26. Fridman JS, Scherle PA, Collins R, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. J Immunol. 2010;184(9):5298-5307.
27. Kuriya B, Cohen MD, Keystone E. Baricitinib in rheumatoid arthritis: evidence-to-date and clinical potential. Ther Adv Musculoskelet Dis. 2017;9(2):37-44.
28. Shi JG, Chen X, Lee F, et al. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. J Clin Pharmacol. 2014;54(12):1354-1361.
29. Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Rheumatol. 2017;69(3):506-517.
30. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376(7):652-662.
31. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017;76(1):88-95.
32. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med. 2016;374(13):1243-1252.
33. Genovese M, Smolen J, Takeuchi K, et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 5.5 years: an updated integrated safety analysis [abstract no. 511]. Arthritis Rheumatol. 2017;69(510):664–666.
34. Semerano L, Decker P, Clavel G, et al. Developments with investigational Janus kinase inhibitors for rheumatoid arthritis. Expert Opin Investig Drugs. 2016;25(12):1355-1359.

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