New insights in the treatment of psoriatic arthritis

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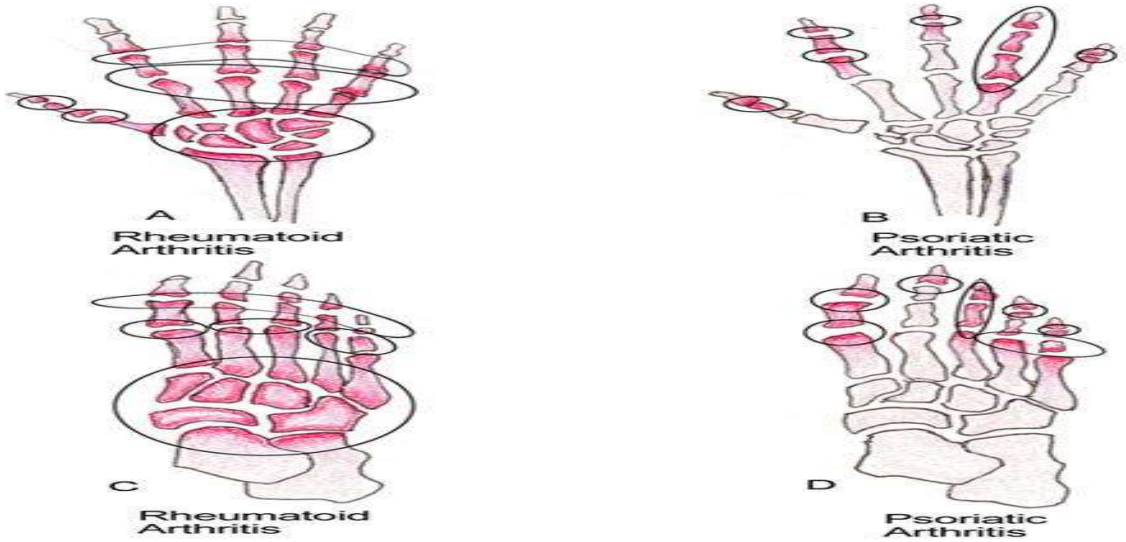
Declaration of interest

I have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

- Psoriatic arthritis is a chronic inflammatory arthropathy that affects approximately 6% to 48% of patients with psoriasis.

- Arthritis is not correlated with the extent of skin disease.



Medical treatment regimens of Psoriatic Arthritis include……

- Nonsteroidal anti-inflammatory drugs (NSAIDs),
- Janus kinase (JAK) inhibitors,
- Disease-modifying antirheumatic drugs (DMARDs). DMARDs include the following :

  Methotrexate

  Sulfasalazine

  Cyclosporine

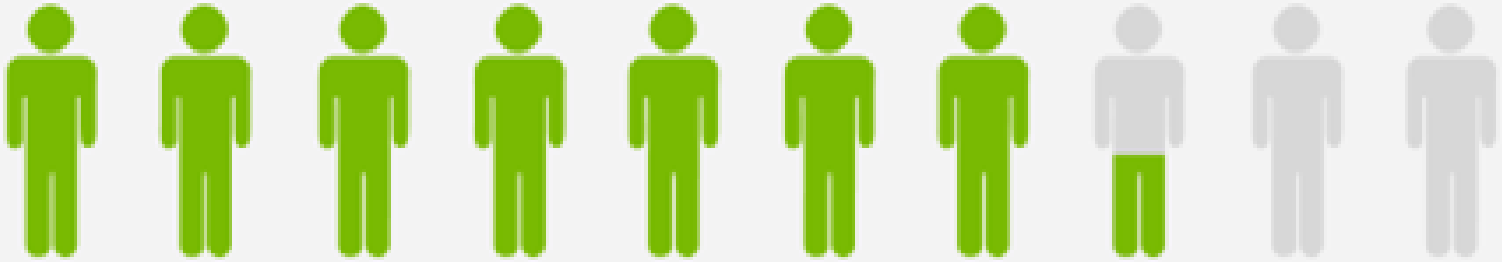
  Leflunomide

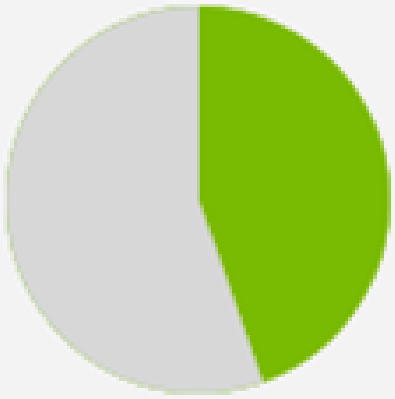
  Biologic agents (eg, TNF, PDE4, or interleukin inhibitors; CD80 binders)

- The mainstay of treatment is biologic therapy (eg, tumor necrosis factor-α inhibitors) in conjunction with disease-modifying antirheumatic drugs.

- Patients with end-stage joint destruction may require surgery to alleviate pain and restore function.

72% of patients with PsA who began therapy with an oral DMARD changed therapy.[30]





45% of patients with psoriatic arthritis were dissatisfied with their treatment.[10]

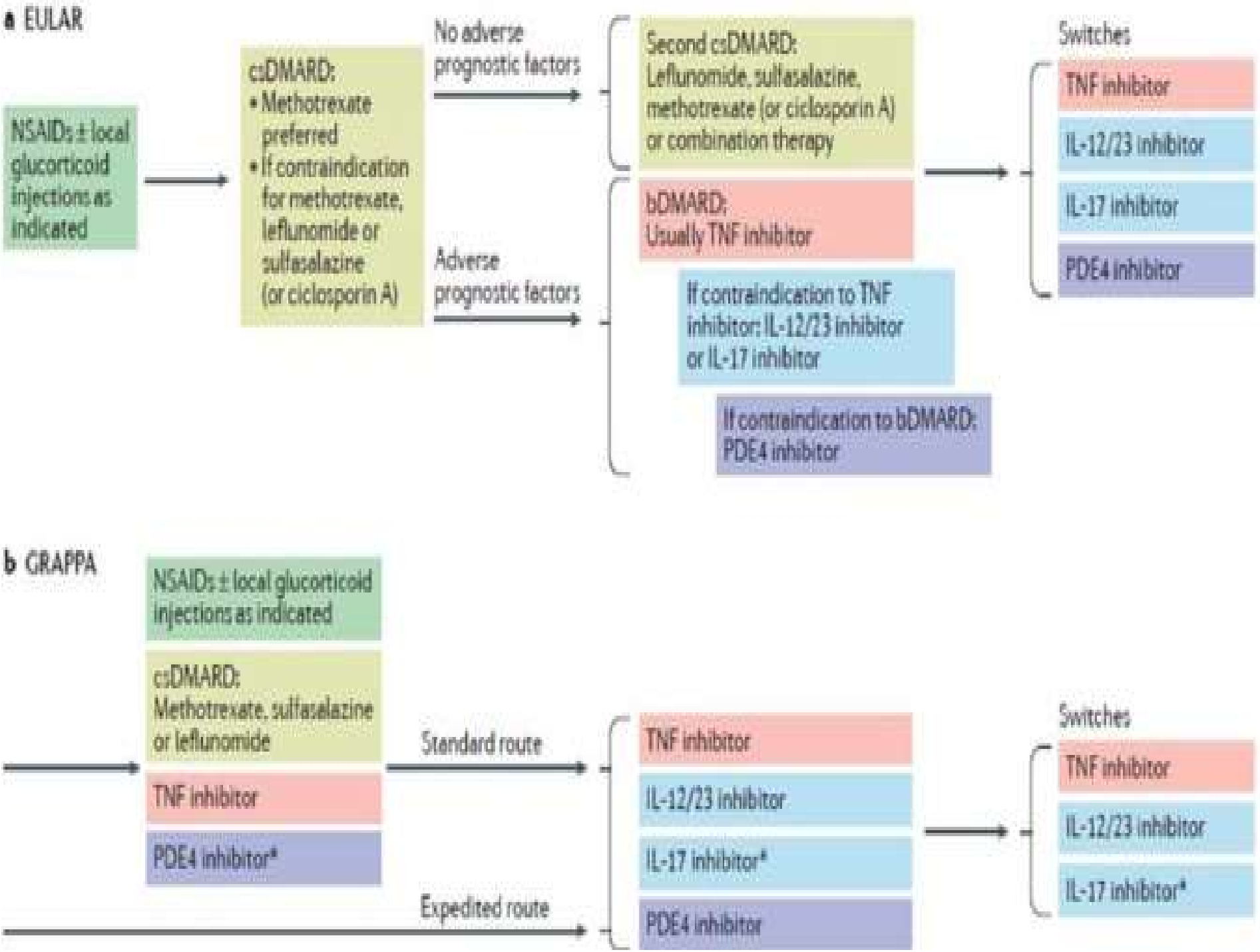
The approach to treatment is generally consistent with recommendations from several major groups, although these vary somewhat depending in part upon the dates when several agents became available for use in clinical practice.

RECOMMENDING ORGANIZATIONS ARE…..

- GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis)
- EULAR (European League Against Rheumatism)
- American College of Rheumatology(ACR)
- Canadian Rheumatology Association and Spondyloarthritis Research Consortium
- International treat-to-target task force on axial and peripheral spondyloarthritis and psoriatic arthritis

EULAR 2015 recommendations for the management of psoriatic arthritis with pharmacological therapies

- **If a TNF inhibitor is not appropriate, consider IL-12/23 or IL-17 inhibitor for patients with peripheral arthritis and one csDMARD failure;**
- **If a TNF inhibitor or IL-12/23 or an IL-17 inhibitor is not appropriate, consider a PDE-4 inhibitor (apremilast) as bDMARD of choice;**
- **For active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections, consider TNF inhibitor as a first bDMARD of choice;**
- **In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, a TNF inhibitor shall be used as a bDMARD of choice (csDMARDs not recommended**);
- **In patients who failed a bDMARD, switching to another bDMARD should be considered, including switching between TNF inhibitors**


a EULAR
NSAIDs ± local glucorticoid injections as indicated
csDMARD:
• Methotrexate preferred
• If contraindication for methotrexate, leflunomide or sulfasalazine (or ciclosporin A)
No adverse prognostic factors
Adverse prognostic factors
Second csDMARD: Leflunomide, sulfasalazine, methotrexate (or ciclosporin A) or combination therapy
bDMARD: Usually TNF inhibitor
If contraindication to TNF inhibitor: IL-12/23 inhibitor or IL-17 inhibitor
If contraindication to bDMARD: PDE4 inhibitor
Switches
TNF inhibitor
IL-12/23 inhibitor
IL-17 inhibitor
PDE4 inhibitor
b GRAPPA
NSAIDs ± local glucorticoid injections as indicated
csDMARD: Methotrexate, sulfasalazine or leflunomide
TNF inhibitor
PDE4 inhibitor*
Standard route
Expedited route
TNF inhibitor
IL-12/23 inhibitor
IL-17 inhibitor*
PDE4 inhibitor
Switches
TNF inhibitor
IL-12/23 inhibitor
IL-17 inhibitor*

Arthritis & Rheumatology
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SPECIAL ARTICLE 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis

Jasvinder A. Singh,1 Gordon Guyatt,2 Alexis Ogdie,3 Dafna D. Gladman,4 Chad Deal,5 Atul Deodhar,6 Maureen Dubreuil,7 Jonathan Dunham,3 M. Elaine Husni,5 Sarah Kenny,8 Jennifer Kwan-Morley,9 Janice Lin,10 Paula Marchetta,11 Philip J. Mease,12 Joseph F. Merola,13 Julie Miner,14 Christopher T. Ritchlin,15 Bernadette Siaton,16 Benjamin J. Smith,17 Abby S. Van Voorhees,18 Anna Helena Jonsson,13 Amit Aakash Shah,19 Nancy Sullivan,20 Marat Turgunbaev,19 Laura C. Coates,21 Alice Gottlieb,22 Marina Magrey,23 W. Benjamin Nowell,24 Ana-Maria Orbai,25 Soumya M. Reddy,26 Jose U. Scher,26 Evan Siegel,27 Michael Siegel,28 Jessica A. Walsh,29 Amy S. Turner,19 and James Reston20

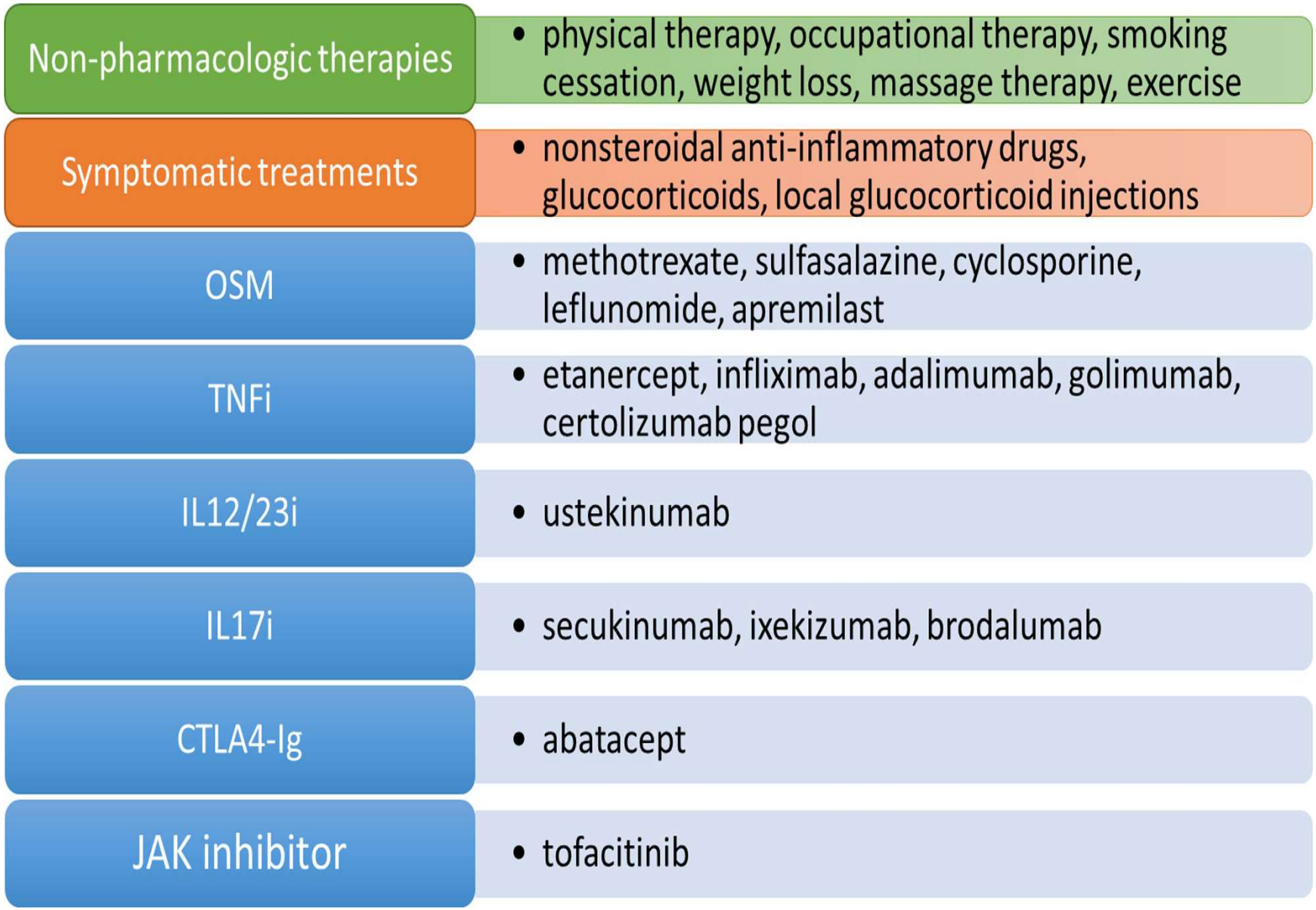
Non-pharmacologic therapies
• physical therapy, occupational therapy, smoking cessation, weight loss, massage therapy, exercise
Symptomatic treatments
• nonsteroidal anti-inflammatory drugs, glucocorticoids, local glucocorticoid injections
OSM
• methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast
TNFi
• etanercept, infliximab, adalimumab, golimumab, certolizumab pegol
IL12/23i
• ustekinumab
IL17i
• secukinumab, ixekizumab, brodalumab
CTLA4-Ig
• abatacept
JAK inhibitor
• tofacitinib

Table 4. Efficacy and Side Effects of Drugs for the Treatment of Psoriatic Arthritis.

Drug (Mode of Administration)	Dose According to Site		Signs and Symptoms		Structural Modification of Joints*	Common Side Effects
	Joints	Skin	Joints	Skin		
NSAIDs			Mild response	—	Not assessed	
Naproxen (oral)	750–1000 mg/day	Not applicable				Gastrointestinal effects
Diclofenac (oral)	100–150 mg/day	Not applicable				Cardiac effects
Indomethacin (oral)	100/150 mg/day	Not applicable				Renal effects
DMARDs						
Methotrexate (oral or SC)	15–25 mg/wk	15–25 mg/wk	Mild response	Moderate response	Not assessed	Hair loss, nausea, hepatic effects
Leflunomide (oral)	20 mg/day	Not applicable	Mild response	Mild response	Not assessed	Diarrhea, renal effects, hair loss
Sulfasalazine (oral)	2–3 g/day	Not applicable	—	—	Not assessed	Neutropenia, diarrhea
Anti-TNF agents						
Adalimumab (SC)	40 mg every 2 wk	80 mg loading dose, 40 mg 1 wk later, then 40 mg every 2 wk	Very good response	Moderate response	Moderate response	Injection-site reactions, infections
Certolizumab (SC)	200 mg every 2 wk or 400 mg every 4 wk	Not applicable	Very good response	Moderate response	Moderate response	Injection-site reactions, infections
Etanercept (SC)	50 mg weekly	50 mg twice/wk	Very good response	Mild response	Moderate response	Injection-site reactions, infections
Golimumab (SC, infusion)	50 mg monthly	Not applicable	Very good response	Mild response	Moderate response	Injection-site reactions, infections
Infliximab (infusion)	5 mg/kg of body weight at 0, 2, and 6 wk, then every 8 wk	5–10 mg/kg at 0, 2, and 6 wk, then every 8 wk	Very good response	Excellent response	Moderate response	Infusion reactions, infections
Anti–interleukin-17 agents						
Ixekizumab (SC)	80 mg every 2 wk	80 mg every 2 wk	Very good response	Excellent response	Mild response	Candida infections
Secukinumab (SC)	150 mg weekly from 0–4 wk, then monthly	300 mg weekly from 0–4 wk, then monthly	Very good response	Excellent response	Mild response	Candida infections
Anti–interleukin-12–interleukin-23 agent: ustekinumab (SC)	45 mg/kg (for body weight of <100 kg) or 90 mg/kg (for body weight of ≥100 kg) at 0, 4, and 12 wk, then every 12 wk	45 mg/kg (for body weight of <100 kg) or 90 mg/kg (for body weight of ≥100 kg) at 0, 4, and 12 wk, then every 12 wk	Very good response	Very good response	Mild response	Injection-site reactions, infections
PDE4 inhibitor: apremilast (oral)	30 mg twice daily	30 mg twice daily	Moderate response	Mild response	Not assessed	Weight loss, diarrhea

* Recent trials of these agents involved patients with little disease progression, resulting in a smaller effect on structural modification as compared with earlier trials, which involved patients with more severe disease and more progression. For drugs that were not assessed with respect to structural modification of joints, observational data suggest no response. Dashes indicate that there was no appreciable response. DMARDs denotes disease-modifying antirheumatic drugs, NSAIDs nonsteroidal antiinflammatory drugs, PDE4 phosphodiesterase 4, SC subcutane-

PSORIATIC ARTHRITIS TREATMENT MARKET

North America Psoriatic Arthritis Treatment Market Size, 2018

Global Psoriatic Arthritis Treatment Market, By Drug Class, 2018

Global Psoriatic Arthritis Treatment Market Size (US$ Mn), 2018 to 2026

2018	5,793.3 Mn

2026	12,175.2 Mn

- Cochrane Database Syst Rev. 2018 Jun; 2018(6): CD013043.
- Published online 2018 Jun 13. doi: 10.1002/14651858.CD013043
- PMCID: PMC6513028

- Interleukin inhibitors for psoriatic arthritis

- Gaurav Sharma, Amy S Mudano, and Jasvinder A Singh

TNF inhibitor use and efficacy

The five original TNF inhibitors and their respective dosing regimens are:
●Etanercept – 50 mg as a subcutaneous injection once weekly. An initial dose of 50 mg twice weekly for the first three months.
●Infliximab – 5 mg/kg administered by intravenous infusion at zero, two, and six weeks, followed by 5 mg/kg every eight weeks thereafter. It may be given either with or without MTX.
●Adalimumab – 40 mg subcutaneously once every two weeks. Adalimumab is a human monoclonal anti-TNF antibody.
●Golimumab – 50 mg subcutaneously once monthly. Golimumab is a human monoclonal anti-TNF antibody.
●Certolizumab pegol – Initial dose of 400 mg (administered as two 200 mg injections subcutaneously), with this dose repeated two and four weeks after the initial dose; maintenance with 200 mg once every other week, but may alternatively treat with 400 mg every four weeks. .

Several clinical trials and studies have proven the benefit of TNF-alpha inhibitors in treating PsA (Heiberg 2007; Saad 2008). Regarding the benefit and adverse effect profile, it seems that adalimumab, etanercept, golimumab, and infliximab are equally beneficial (Fénix-Caballero 2013).

Despite their proven benefit in PsA, a number of patients with psoriatic arthritis treated with TNF-alpha inhibitors fail to respond, some develop resistance and some have serious adverse effects (Davari 2014), though they rarely cause the development of unusual side effects such as vasculitis (Gaudio 2013; Hemmati 2013).

There is, therefore, a need for therapeutic agents with a different mechanism of action, a better adverse effects profile and an ability to prevent progression of joint damage.

Treatment of psoriatic arthritis

Authors:Dafna D Gladman, MD, FRCP,C Christopher Ritchlin, MD, MPH
Section Editor: Joachim Sieper, MD Deputy Editor: Paul L Romain, MD, Contributor

Disclosures
All topics are updated as new evidence becomes available and after peer review process.

Literature review current through: **Sep 2019.** | This topic last updated: **Nov 20, 2018.**

Emerging Therapies

Ustekinumab has been licensed for PSA.

A human monoclonal antibody which blocks a signalling pathway in the disease by preventing IL-12 and IL-23 from binding to IL-12Rβ1.

Apremilast, a new oral, targeted, synthetic DMARD has been licensed, which targets phosphodiesterase 4.

It offers a number of advantages over conventional DMARDs
low toxicity and
lack of monitoring need,
but its efficacy in practice has yet to be fully evaluated.

Secukinumab

Fully human anti-IL-17A monoclonal antibody.

In a phase III study, it was significantly more effective than placebo in improving the signs and symptoms of PsA, along with patient-reported physical functioning and quality of life.

There was also a significant reduction in radiographic progression in the treatment group compared with the placebo group.

First anti-IL-17 based therapy to receive FDA approval for treatment of PsA in January 2016.

Ixekizumab

- Humanized anti-IL-17A monoclonal antibody.
- Studied in active PsA in a recent 24-week phase III trial (SPIRIT-P1), comparing subcutaneous ixekizumab to subcutaneous adalimumab or placebo in PsA patients who were naive to biologic DMARDs.
- Significantly more patients receiving ixekizumab achieved a greater ACR20 response as compared to placebo, and treatment also reduced radiographic progression of joint damage.
- This trial has been extended by 3 years to allow for longer-term assessment of safety and efficacy

Brodalumab

Fully human IL-17R monoclonal antibody.

Evaluated in PsA patients in a placebo-controlled phase II study. At week 12 of treatment, patients receiving brodalumab demonstrated significantly higher rates of improvement in ACR20 than the placebo group.

References:

1. Wang EA, Suzuki E, Maverakis E, Adamopoulos IE. Targeting IL-17 in psoriatic arthritis. *Eur J Rheumatol*. Published online Nov. 10, 2017. DOI: 10.5152.eurjrheum.2017.17037

Home Rheumatology
Fine-Tuning the Treatment of Psoriatic Arthritis: Focus on the IL-23 Pathway

29 JULY 2019 | RHEUMATOLOGY

European Congress of Rheumatology 2019 in Madrid, Spain

Chairpeople:

Georg Schett,[1] Peter Taylor[2]

Speakers:

Lluís Puig,[3] Georg Schett, Stefan Siebert,[4] Peter Taylor

Meeting Summary

The symposium **‘Fine-tuning the treatment of PsA: Focus on the IL-23 pathway’ took place during the 2019 European League Against Rheumatism (EULAR) Annual Congress in Madrid, Spain.**

The presentations covered the rationale for targeting IL-23 in psoriatic arthritis (PsA), details of the IL-23 pathway relevant to psoriatic disease, practical implications and consequences of targeting IL-23

Prof Peter Taylor discussed the practical implications of targeting IL-23 and provided more details about the specific effects of targeting not only IL-23 (with risankizumab, tildrakizumab, or guselkumab) but also IL-12/23 (with ustekinumab) and IL-17 (with ixekizumab, secukinumab, or brodalumab).

In the final presentation, Prof Lluís Puig described clinical experience of targeting IL-23 in psoriasis and provided an overview of findings from several clinical trials, including: VOYAGE 1 and 2 (guselkumab versus the TNF inhibitor [TNFi] adalimumab); NAVIGATE (guselkumab versus ustekinumab); and the head-to-head ECLIPSE study (guselkumab versus secukinumab).

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RheumaNow.

Updates on Psoriatic Arthritis at ACR 2018

By Philip Gardiner | 24 October 2018

Memorable annual conferences are usually marked by a key focus on an emerging area of interest. I think 2018 was the year that belonged to psoriatic arthritis.

For a long time we thought that the treatments for PsA were just the same as RA since we were treating the same problem of synovitis.

One of the sessions this year was aptly entitled 'RA and PsA – the great divorce'.

THE LANCET

ARTICLES| VOLUME 382, ISSUE 9894, P780-789, AUGUST 31, 2013

Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial

Dr Iain B McInnes, MD †Prof Arthur Kavanaugh, MD †Alice B Gottlieb, MD,Lluís Puig, MD,Proton Rahman, MD,Christopher Ritchlin, MD,et al.

Published:June 13, 2013 DOI:https://doi.org/10.1016/S0140-6736(13)60594-2

Interpretation

Ustekinumab significantly improved active psoriatic arthritis compared with placebo, and might offer an alternative therapeutic mechanism of action to approve biological treatments

Drug Safety
June 2019, Volume 42, Issue 6, pp 751–768|

Ustekinumab Safety in Psoriasis, Psoriatic Arthritis, and Crohn's Disease: An Integrated Analysis of Phase II/III Clinical Development Programs

Subrata Ghosh,Lianne S. Gensler,Zijiang Yang,Chris Gasink,Soumya D. Chakravarty,Kamyar Farahi,Paraneedharan Ramachandran,Elyssa Ott,Bruce E. Strober.

Conclusions

Ustekinumab demonstrated a favorable and consistent safety profile across registrational trials in approved indications.

Arthritis Research & Therapy

Long-Term Experience With Apremilast in Patients With Psoriatic Arthritis

- **5-Year Results From a Palace 1-3 Pooled Analysis**

- Arthur Kavanaugh; Dafna D. Gladman; Christopher J. Edwards; Georg Schett; Benoit Guerette; Nikolay Delev; Lichen Teng; Maria Paris; Philip J. Mease
  Arthritis Res Ther. 2019;21(118)

Conclusions

Apremilast maintained clinical benefit and a favorable safety profile for up to 5 years among patients with PsA.

BMJ Journals
Volume 4, Issue 2
Original article

Ixekizumab is efficacious when used alone or when added to conventional synthetic disease-modifying antirheumatic drugs (cDMARDs) in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor inhibitors

Peter Nash, Frank Behrens, Ana-Maria Orbai, Suchitrita S Rathmann, David H Adams, Olivier Benichou and Atul Deodhar

Conclusion

Ixekizumab was efficacious in patients with active PsA and previous tumour necrosis factor inhibitor (TNFi) inadequate response or TNFi intolerance treated with ixekizumab alone or when added to cDMARDs

Published online 2018 Sep 6.
doi: 10.1177/1759720X18787766PMCID: PMC6130093PMID: 30210583

The role of secukinumab in the treatment of psoriatic arthritis and ankylosing spondylitis

Leticia Garcia-Montoya and **Helena Marzo-Ortega**

Conclusion

Secukinumab is an anti-IL-17A monoclonal antibody that has demonstrated efficacy in the treatment of PsA and AS.

Considering the good safety profile and medium-term drug survival, secukinumab is likely to play a relevant role in the management of these diseases.

Real-life, long-term exposure will help elucidate the positioning of this drug within treatment algorithms in PsA and AS.

Tofacitinib in the management active psoriatic arthritis: patient selection and perspectives

Authors Ly K, Beck KM, Smith MP, Orbai AM, Liao W

Received 4 April 2019

Accepted for publication 23 August 2019

Published 28 August 2019 Volume 2019:9 Pages 97—107

DOI https://doi.org/10.2147/PTT.S161453

Review by Single-blind

Conclusion

Tofacitinib is an efficacious treatment option for patients with PsA as demonstrated in two placebo-Controlled phase III RCTs using the ACR response definitions and the HAQ-DI.

In addition, **tofacitinib improved patient reported outcomes and radiographic non-progression in patients with PsA.**

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Immunotherapy. 2017 Nov;9(14):1153-1163.
doi: 10.2217/imt-2017-0087. Epub 2017 Oct 2.

Tofacitinib in psoriatic arthritis.

Wang TS[1,2], Tsai TF[2].

Author information

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2Department of Dermatology, National Taiwan University Hospital & National Taiwan University College of Medicine, Taipei, Taiwan.

Conclusions

- **Both tofacitinib 5 or 10 mg twice a day were superior to placebo for American College of Rheumatology 20% improvement criteria response at 3 months.**

- **Showed significant improvement of skin, enthesitis and dactylitis.**
- **Tofacitinib is a promising treatment option for psoriatic arthritis.**

Rheumatol Ther. 2018 Dec;5(2):567-582. doi: 10.1007/s40744-018-0131-5. Epub 2018 Nov 9.

Efficacy of Tofacitinib for the Treatment of Psoriatic Arthritis: Pooled Analysis of Two Phase 3 Studies.

Nash P[1], Coates LC[2], Fleischmann R[3], Papp KA[4], Gomez-Reino JJ[5], Kanik KS[6], Wang C[6], Wu J[6], Menon S[6], Hendrikx T[7], Ports WC[6].

CONCLUSIONS:

In a pooled analysis of csDMARD-IR/TNFi-naïve and TNFi-IR patients, **tofacitinib was superior to placebo at month 3 across four PsA domains: peripheral arthritis, psoriasis, enthesitis and dactylitis.**

RHEUMATOLOGY

October 19, 2017

N Engl J Med 2017; 377:1525-1536

DOI: 10.1056/NEJMoa1615977

Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors

Dafna Gladman, M.D., William Rigby, M.D., Valderilio F. Azevedo, M.D., Ph.D., Frank Behrens, M.D., Ricardo Blanco, M.D., Andrzej Kaszuba, M.D., Ph.D., Elizabeth Kudlacz, Ph.D., Cunshan Wang, Ph.D., Sujatha Menon, Ph.D., Thijs Hendrikx, Ph.D., and Keith S. Kanik, M.D.

CONCLUSIONS

Patients with active psoriatic arthritis who had had an inadequate response to TNF inhibitors,tofacitinib was more effective than placebo over 3 months in reducing disease activity.

June 2018 - Volume 77 - 6
BMJ Journals
Clinical and epidemiological research

Extended report

Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study

Philip Mease, Désirée van der Heijde, Robert L andewé, Shephard Mpofu, Proton Rahman, Hasan Tahir, Atul Singhal, Elke Boettcher Sandra Navarra, Karin Meiser, Aimee Readie, Luminita Pricop, Ken Abrams

Conclusion

S.c. secukinumab 300 mg and 150 mg with and without LD **significantly improved clinical signs and symptoms and inhibited radiographic structural progression versus placebo at week 24 in patients with PsA**.

Yoga Is The Best Psoriatic Arthritis Treatment

Yoga is one proven method of reducing and eliminating pain. stretching and a hot shower are also a way to relax muscles before exercise or yoga. Make sure to apply ice afterwards to help reduce post-exercise inflammation. Remember, exercises should be performed on a regular basis for the sole purpose of strengthening, maintaining and improving the overall motion of the joints. Even if you do not have psoriatic arthritis, you should be exercising anyway to hopefully prevent getting this disease.

As we age, our muscles tend to not work as they once did. They break down more easily and can tear when you least expect it. Getting into a regular routine to exercise can be very helpful to the muscles and joints. Drink more water than you usually do to keep the joints lubricated. Continue to strengthen those muscles and bring back the youth in your body.

Take Note

- A treat-to-target approach has gained traction and has increasingly made remission of PsA the main goal of treatment

- A phased treatment algorithm provides a graduated approach, starting with nonbiologics and proceeding to biologics only if they’re needed.

- The update, which takes the cost of drugs into account, provides physicians with an important tool to justify their use of the new treatment options.

THANKS ALL