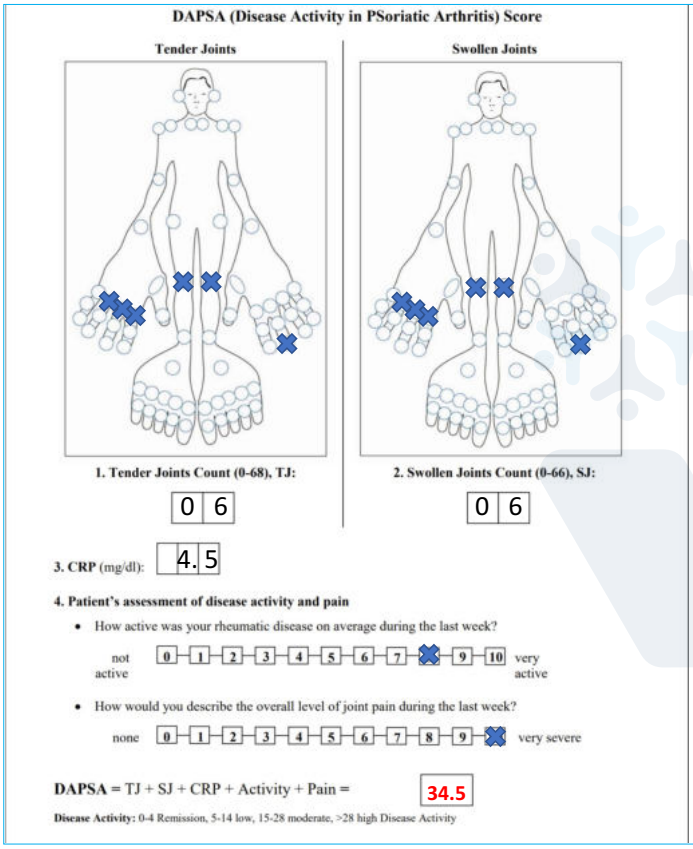
Vai trò của kháng TNF alpha trong điều trị viêm khớp vảy nến từ các khuyến cáo.

BSCK2 TRẦN NGỌC HỮU ĐỨC

Trường hợp lâm sàng

- BN nam, 1968
- Địa chỉ: TP. HCM
- Nghề nghiệp: thợ may
- Theo dõi tại Đơn vị Điều trị trong ngày, khoa Nội Khớp, BV Chợ Rẫy
- Giữa 2018: đau, sưng nhiều khớp ngoại biên được chẩn đoán viêm khớp dạng thấp được điều trị tại Bs tư: etoricoxib 90mg/ngày, MTX 2.5mg 4 viên/tuần, bệnh giảm ít
- 8/2019: vẩy nến kín đáo vùng rốn và da đầu→ Δ Viêm khớp vẩy nến
- BN khám và điều trị BS tư tiếp tục: etoricoxib 90mg/ngày, MTX 2.5mg 5 viên/tuần → Đau khớp giảm ít, vẩy nến ngày càng nhiều



DAPSA (Disease Activity in PSoriatic Arthritis) Score

Tender Joints

Swollen Joints

1. Tender Joints Count (0-68), TJ: 0 6

2. Swollen Joints Count (0-66), SJ: 0 6

3. CRP (mg/dl): 4.5

4. Patient's assessment of disease activity and pain

- How active was your rheumatic disease on average during the last week?

not active 0 1 2 3 4 5 6 7 8 9 10 very active

- How would you describe the overall level of joint pain during the last week?

none 0 1 2 3 4 5 6 7 8 9 very severe

DAPSA = TJ + SJ + CRP + Activity + Pain = 34.5

Disease Activity: 0-4 Remission, 5-14 low, 15-28 moderate, >28 high Disease Activity

Khám LS + CLS

- BN tỉnh, tiếp xúc tốt
- ***Ngồi xe lăn*** (do đau khớp gối nhiều)
- Thể trạng gầy, BMI: 19.11
- Vảy nến rải rác toàn thân và da đầu, BSA # 6%
- Tổn thương móng tay, móng chân
- **Công thức máu:**
  - HC: 4.64 T/L, Hb: 11.6 g/dl
  - BC: 7 G/L, Neu: 61.8%
- **Sinh hoá máu:**
  - ALT: 40 U/L, AST: 23 U/L (< 35 U/L)
  - BUN: 14 mg/dl, creatinin: 0.92 mg/dl, Ca TP: 2.3 mmol/L
- VS 1h: 85 mm, VS 2h: 120 mm, CRP: 45 mg/L (< 5 mg/l)
- RF (-)
- HBsAg (-), AntiHBc IgM (-); Anti HCV (-)
- IGRA (-)
- Xquang phổi: bình thường

Diễn tiến

- BN dùng golimumab 50 mg/4 tuần
- Lâm sàng đáp ứng ổn , đạt lui bệnh kéo dài
- Cuối 2020 được giãn liều thành 1 lọ mỗi 2 tháng (DAPSA 2.13)
- Cuối 2021 được giãn liều thành 1 lọ mỗi 3 tháng (DAPSA 2.38)
- Lần khám sau cùng 23/9/2022 DAPSA 10.3 (LDA)

Vấn đề

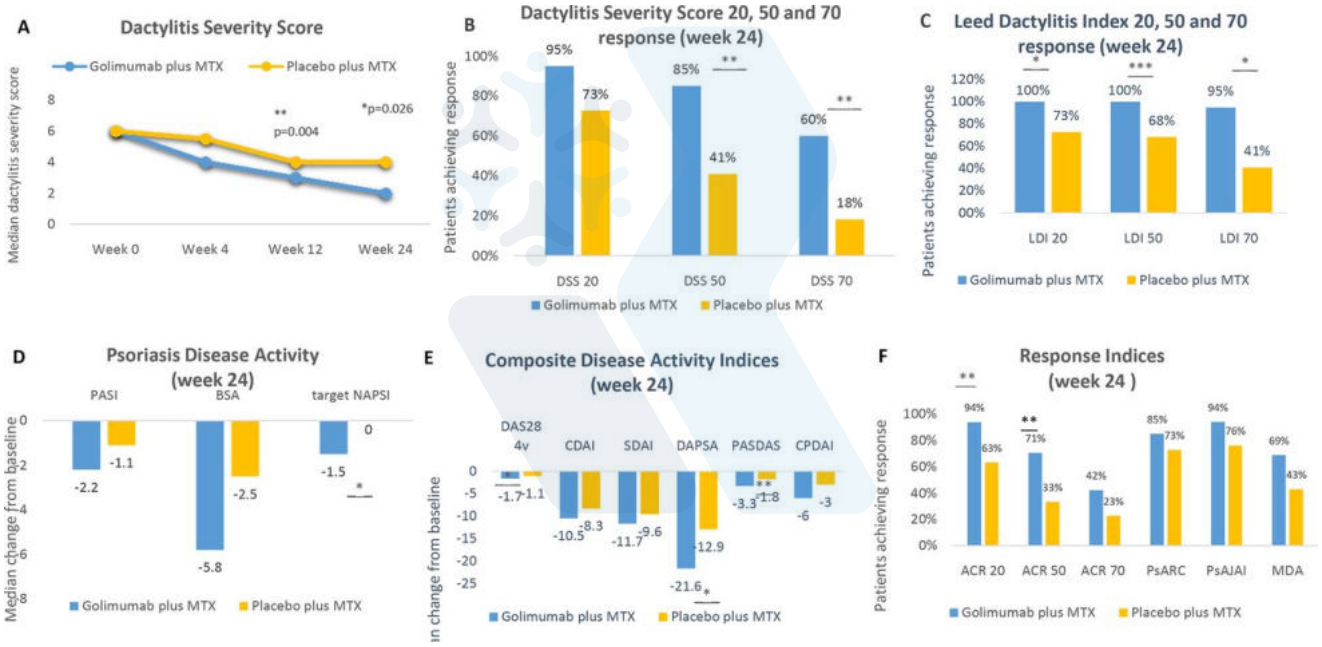
- Khi nào nên khởi đầu thuốc sinh học?
- Thuốc nào ưu tiên?
- Điều trị theo mục tiêu?
- Khi nào giảm/dãn liều?

Vấn đề

- Theo bạn, trong điều trị VKVN, khi nào nên khởi đầu thuốc sinh học?
  A. Sau khi thất bại với csDMARD
  B. Dùng ngay từ đầu
  C. Ý kiến khác

Nghiên cứu GO-DACT

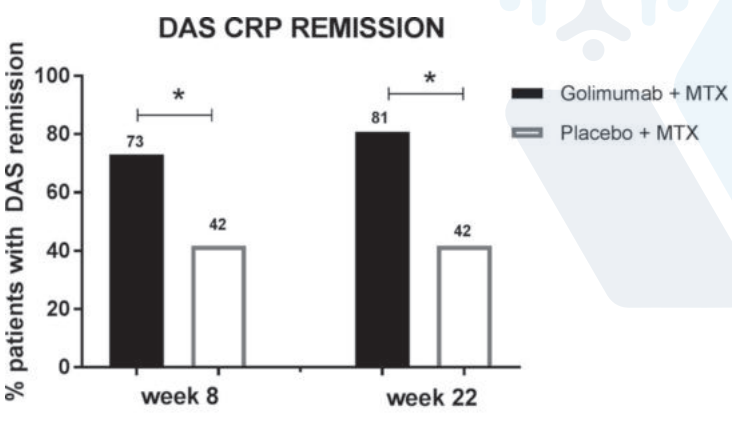
Bn chưa từng dùng csDMARD hay bDMARD được phân ngẫu nhiên thành nhóm dùng GOL + MTX (21) và nhóm PBO + MTX (23).

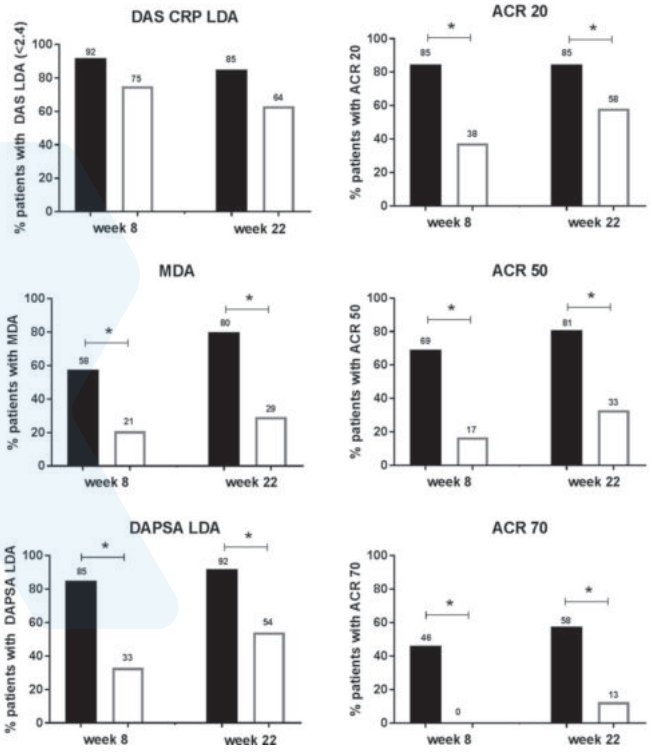


Annals of the Rheumatic Diseases 2020;**79:**490-498.

Khởi động TNFi sớm ở BN VKVN chưa dùng csDMARD hay bDMARD

Patients were randomised to golimumab (50 mg SC monthly)+MTX (n=26) (TNFi arm) or matched placebo+MTX (n=25) (MTX arm). MTX was started 15 mg/week and increased to 25 mg/week over 8 weeks.





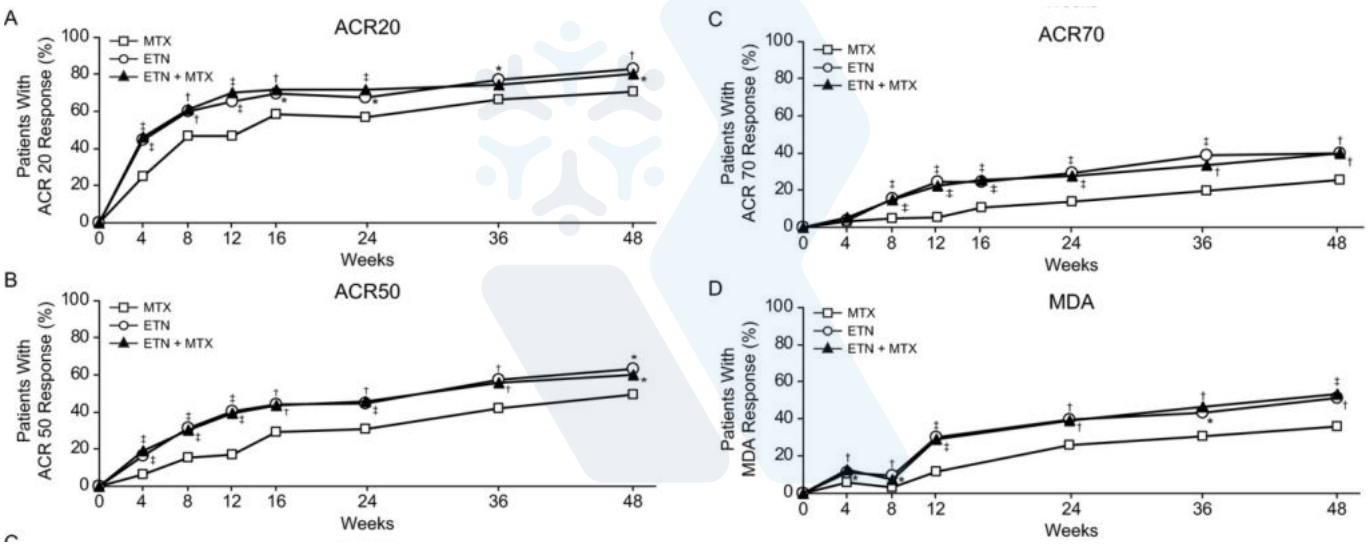
Annals of the Rheumatic Diseases 2019;**78:**610-616.

N/c MIPA: MTX không có hiệu quả trong PsA

Methods. A 6-month double-blind RCT compared MTX (**15 mg/week**) with placebo in active PsA. The primary outcome was PsA response criteria (PsARC). Other outcomes included ACR20, DAS-28 and their individual components. Missing data were imputed using multiple imputation methods. Treatments were compared using logistic regression analysis (adjusted for age, sex, disease duration and, where appropriate, individual baseline scores).
Results. Four hundred and sixty-two patients were screened and 221 recruited. One hundred and nine patients received MTX and 112 received placebo. Forty-four patients were lost to follow-up (21 MTX, 23 placebo). Twenty-six patients discontinued treatment (14 MTX, 12 placebo). Comparing MTX with placebo in all randomized patients at 6 months showed no significant effect on PsARC [odds ratio (OR) 1.77, 95% CI 0.97, 3.23], ACR20 (OR 2.00, 95% CI 0.65, 6.22) or DAS-28 (OR 1.70, 95% CI 0.90, 3.17). **There were also no significant treatment effects on tender and swollen joint counts, ESR, CRP, HAQ and pain. The only benefits of MTX were reductions in patient and assessor global scores and skin scores at 6 months** ($P = 0.03$, $P < 0.001$ and $P = 0.02$, respectively). There were no unexpected adverse events.

Global index	OR (95% CI)	P-value
PsARC	1.77 (0.97, 3.23)	0.06
ACR20 responders	2.00 (0.65, 6.22)	0.23
DAS-28 responders	1.70 (0.90, 3.17)	0.10

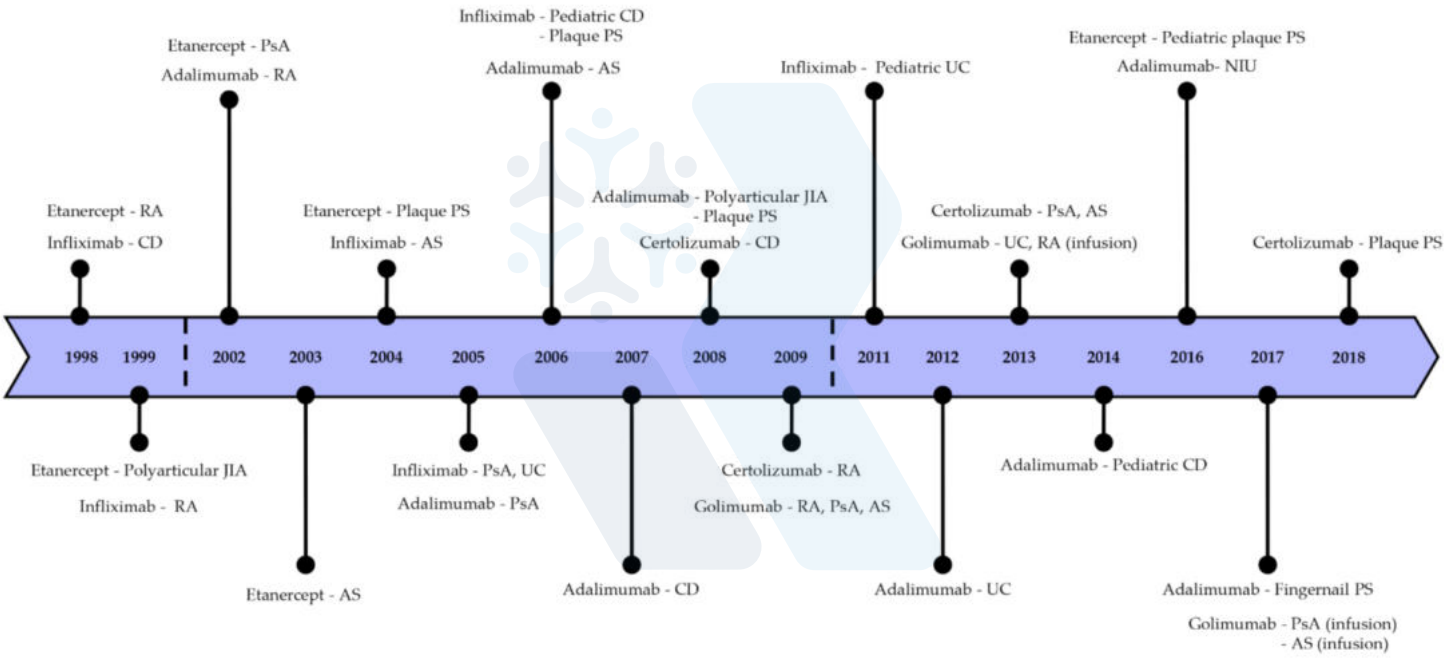
Vai trò của MTX: n/c SEAM PsA



Arthritis Rheumatol . 2019 Jul;71(7):1112-1124. doi: 10.1002/art.40851.

Vấn đề

- Bạn quan tâm điều trị khi lựa chọn thuốc sinh ?
  A. Thuốc nào có nhiều dữ liệu về tính hiệu quả và an toàn
  B. Nghiên cứu head to head
  C. Tổn thương ngoài khớp, bệnh kèm theo
  D. Lựa chọn khác



Int. J. Mol. Sci. 2021, 22, 2719. https://doi.org/10.3390/ijms22052719

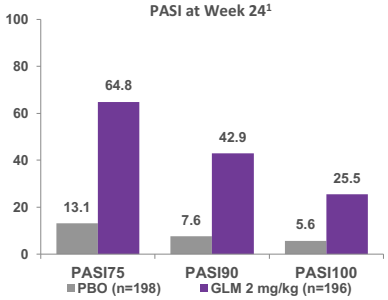
Các TNLS phase 3 quan trọng

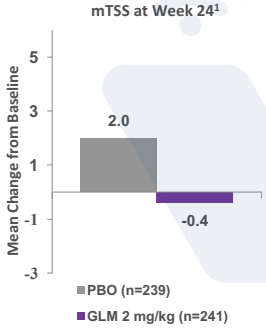
	Reference	Study size (n)	Doses (vs. placebo)	% Achieving ACR20 response (tx/placebo) (primary endpt wk)	% Achieving PASI75 response (tx/placebo) (primary endpt wk)	Inhibition of radiographic progression
Infliximab	IMPACT	104	5 mg/kg IV	65.4/9.6 (16)	68/0 (16)	50 wks
	IMPACT 2	200	5 mg/kg IV	58/11 (14)	64/2 (14)	6 months and 1 yr
Etanercept	12-wk study	60	25 mg SC 2x wk	73/13 (12)	26/0 (12)	Not studied
	24-wk study	205	25 mg SC 2x wk	59/15 (12)	–	12 months and 2 yrs
Adalimumab	ADEPT	313	40 mg SC eow	58/14 (12)	–	24 wks
Golimumab	GO-REVEAL	405	50 mg/100 mg	51/45/9 (14)	40/58/3 (14)	24 wks and 256 wks
Golimumab	GO-VIBRANT	480	2mg/kg IV	76.8/24.3 (24)	64.8/13.1 (24)	24 wks
Certolizumab	RAPID-PsA	409	200 mg/400 mg	58/51.9/24.3 (12)	46.7/47.4/14 (12)	96 wks

Expert Rev Clin Pharmacol. 2017 Aug; 10(8): 899–910.
Kavanaugh et al. J Rheumatol. 2019;46:595-602

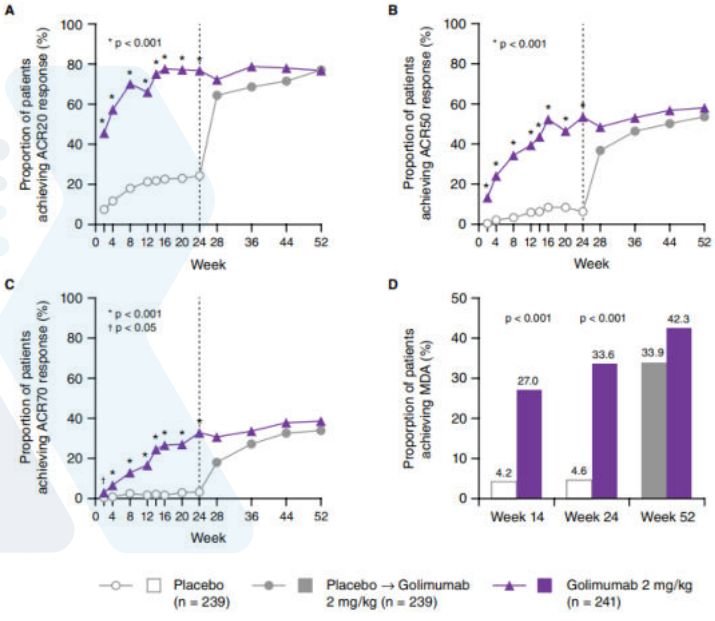
N/c GO-VIBRANT

- BN VKVN hoạt động (≥ 5 khớp sưng đau và CRP ≥ 6 mg/L, đã dùng DMARD ≥ 3 tháng)
- Đánh giá ACR20/50/70, PASI75 và SHS.





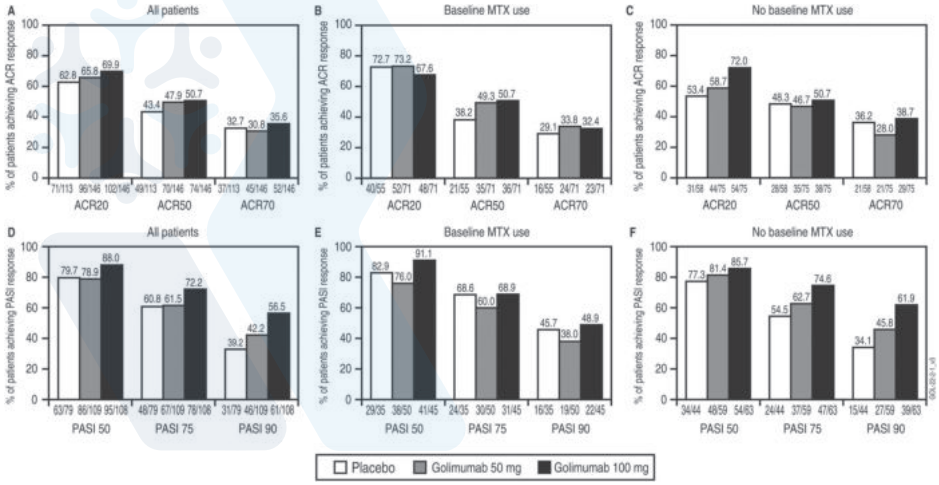
Adapted from Kavanaugh et al. Arthritis Rheumatol 2017;69:2151-61.



Arthritis Care & Research Vol. 72, No. 6, June 2020, pp 806–813

N/c GO-REVEAL sau 256 tuần với golimumab

- Bn VKVN hoạt động (≥ 3 khớp sưng và đau) được phân ngẫu nhiên thành 3 nhóm golimumab 50 mg, golimumab 100 mg và placebo trong 6 tháng. Từ tháng thứ 6 trở đi nhóm placebo được phân ngẫu nhiên thành nhóm golimumab 50 mg và nhóm golimumab 100 mg.
- 126/405 (31%) BN ngưng điều trị tính đến tuần 252.

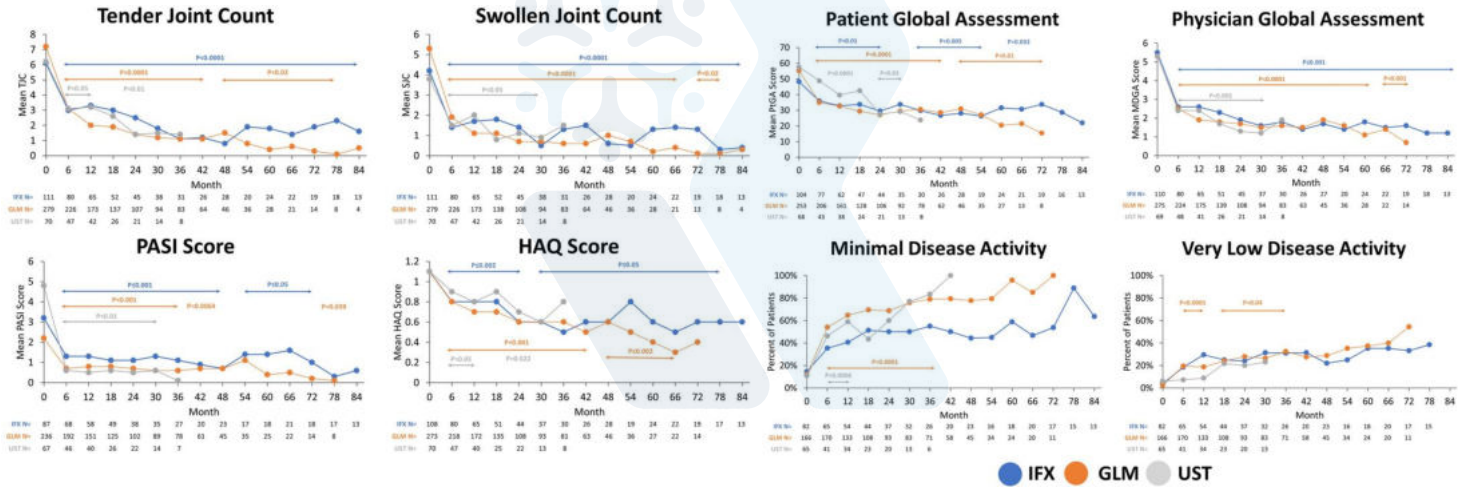


Annals of the Rheumatic Diseases 2014;**73:**1689-1694.

Open access Original research
BMJ Open

Long-term effectiveness and safety of infliximab, golimumab and ustekinumab in patients with psoriatic arthritis from a Canadian prospective observational registry

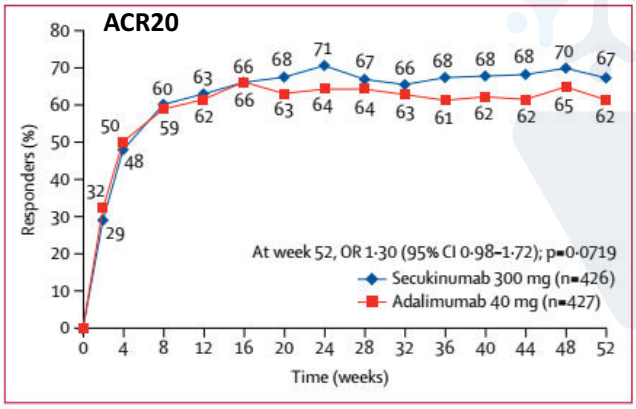
Proton Rahman,[1] Regan Arendse,[2] Majed Khraishi,[1] Dalton Sholter,[3] Maqbool Sheriff,[4] Emmanouil Rampakakis,[5] Allen J Lehman,[6] Francois Nantel [6]

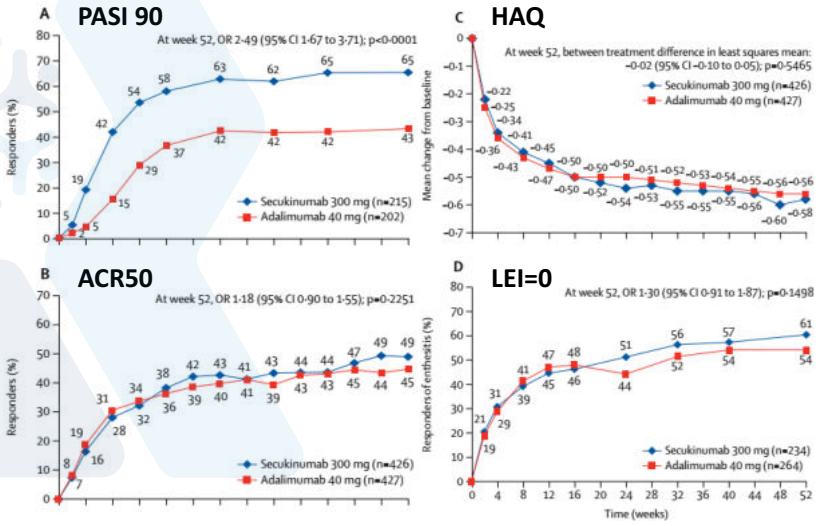


BMC Rheumatol. 2020 Sep 19;4:46. doi: 10.1186/s41927-020-00145-4.

Nghiên cứu EXCEED

… 853 patients to receive secukinumab (n=426) or adalimumab (n=427).
… primary endpoint of superiority of secukinumab versus adalimumab for ACR20 response at week 52 was not met.

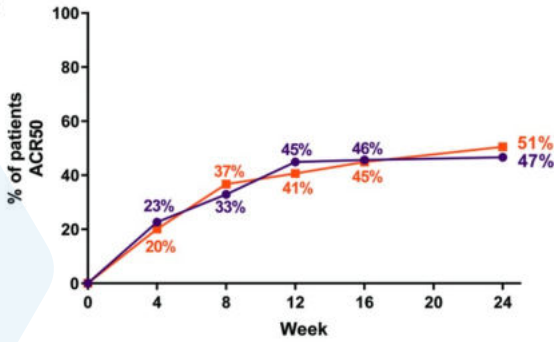


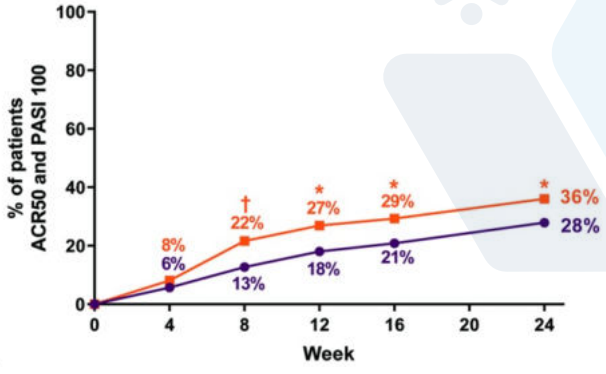


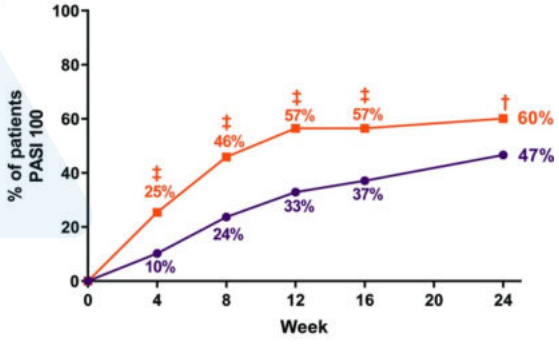
Lancet **395**, 1496–1505 (2020).

Ixekizumab vs adalimumab

Patients with active PsA were randomised (1:1) to approved dosing of IXE or ADA in an open-label, head-to-head, blinded assessor clinical trial. The primary objective was to evaluate whether IXE was superior to ADA at **week 24** for simultaneous achievement of a ≥50% improvement from baseline in the American College of Rheumatology criteria (**ACR50**) **and** a 100% improvement from baseline in the Psoriasis Area and Severity Index (**PASI100**). Major secondary objectives, also at week 24, were to evaluate whether IXE was: (1) non-inferior to ADA for achievement of ACR50 and (2) superior to ADA for PASI100 response. Additional PsA, skin, treat-to-target and quality-of-life outcome measures were assessed at week 24.







Annals of the Rheumatic Diseases 2020;**79:**123-131.

ADA (N=283) IXE (N=283)

The NEW ENGLAND JOURNAL of MEDICINE

Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis

PHASE 3, RANDOMIZED, CONTROLLED TRIAL

1704 Patients with psoriatic arthritis

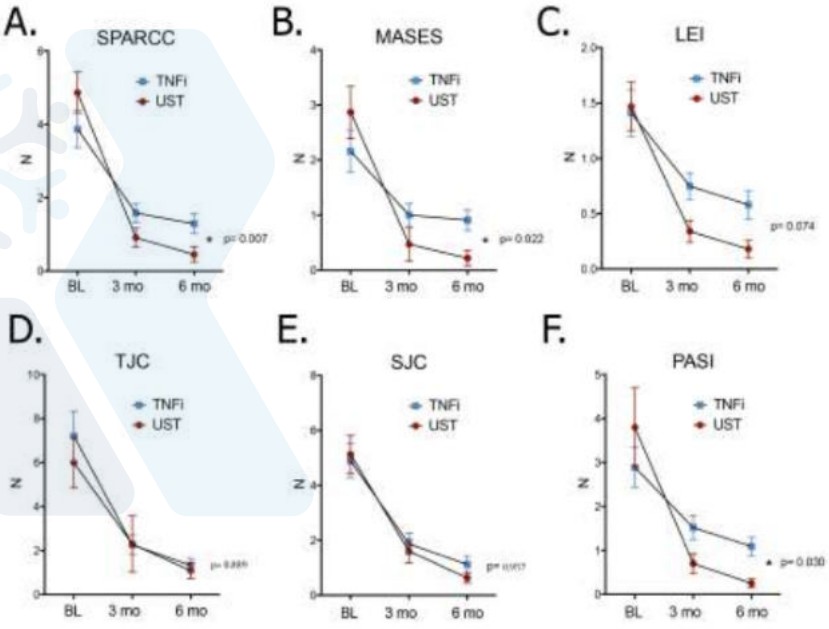
	Upadacitinib 15 mg (once daily) (N=429)	Upadacitinib 30 mg (once daily) (N=423)	Placebo (N=423)	Adalimumab 40 mg (every other week) (N=429)
20% Improvement at week 12 (ACR20 response)	70.6%	78.5%	36.2%	65.0%
	P<0.001 for both upadacitinib doses vs. placebo			
Incidence of adverse events through week 24	66.9%	72.3%	59.6%	64.8%

ACR20 response was greater with upadacitinib than with placebo.
Upadacitinib was noninferior to adalimumab.

I.B. McInnes et al. 10.1056/NEJMoa2022516

N/c ECLIPSA: Ustekinumab vs TNFi

Primary endpoint: SPARCC=0.
51 patients (UST=25; TNFi= 26) were screened, 47 enrolled (UST=23; TNFi=24) and 46 completed the study.
After 24 weeks, 73.9% of UST patients and 41.7% of TNFi patients reached the primary endpoint (SPARCC=0) indicating clearance from enthesitis (p=0.018).
UST achieved superior responses as compared to TNFi with respect to enthesitis (p=0.007) and psoriatic skin disease (p=0.030) but not for arthritis (p=0.95).



The End-to-end Journal (2018), doi: 10.1016/j.semarthrit.2018.05.011

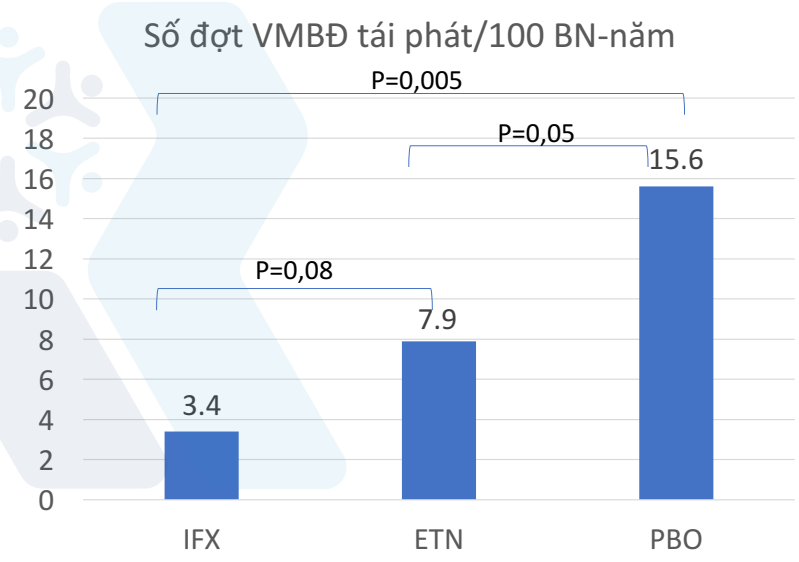
Viêm khớp vảy nến

- Viêm khớp ngoại biên
- Viêm khớp trục
- Viêm điểm bám gân
- Viêm ngón
- Tổn thương da
- Tổn thương móng
- Viêm ruột
- Viêm màng bồ đào

21

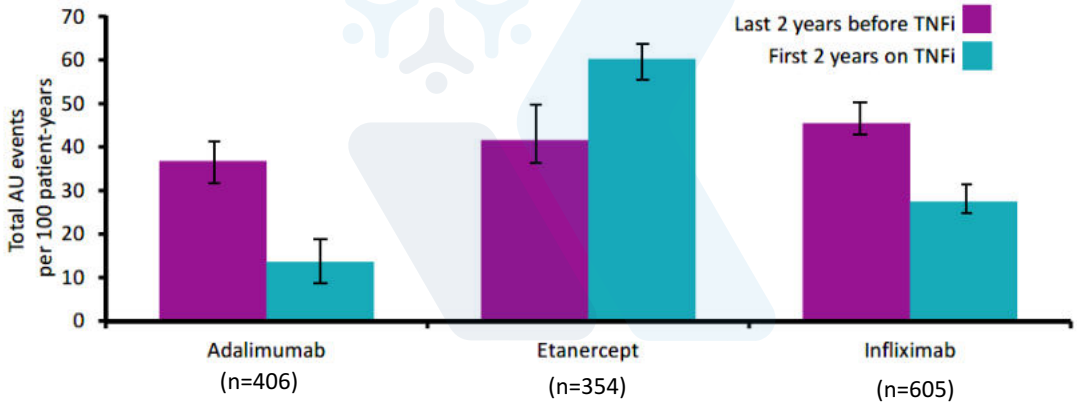
TNFi làm giảm VMBĐ mới mắc ở BN VCSDK

- Dữ liệu từ 4 NC có chứng dùng TNFi trong VCSDK (2 NC ETN, 2 NC IFX) và 3 NC open-label.
- Chọn ra được 397 BN có VMBĐ trong quá trình theo dõi. Trong đó 297 dùng ETN, 90 dùng IFX.



Arthritis Rheum. 2005 Aug; 52(8):2447-51.

Hiệu quả của TNFi lên viêm màng bồ đào: Swedish Biologics Register (ARTIS)

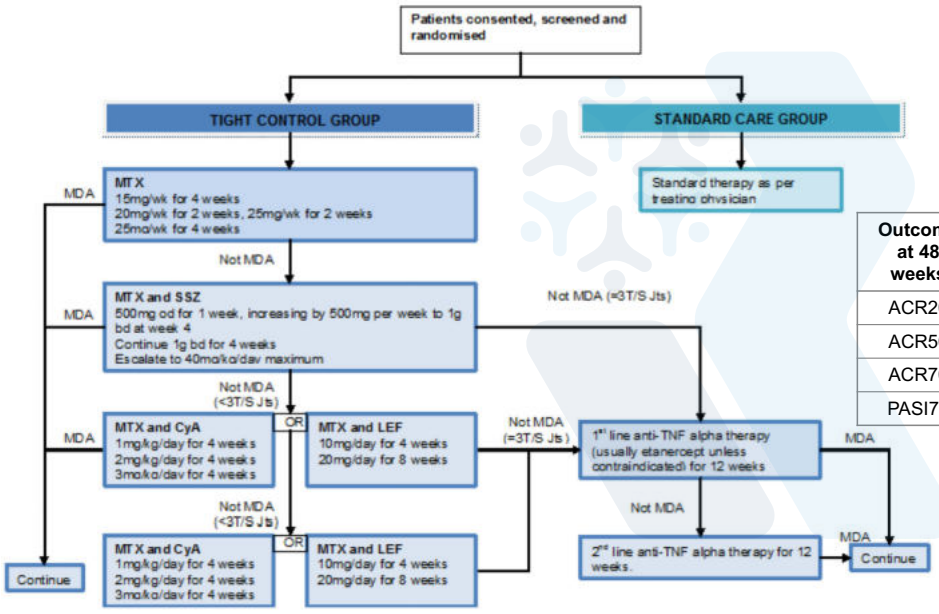


Lie E, et al. Ann Rheum Dis 2017;76:1515–21

Vấn đề

- Có nên điều trị theo mục tiêu?
  - Có
  - Không

Nghiên cứu TICOPA



Outcome at 48 weeks	Tight control n (%)	Standard care n (%)	p-value
ACR20	55/89 (61.8)	37/84 (44.0)	0.0194
ACR50	44/86 (51.2)	21/84 (25.0)	0.0004
ACR70	33/87 (37.9)	15/86 (17.4)	0.0026
PASI75	44/75 (58.7)	27/81 (33·3)	0.0015

Lancet. 2015 December 19; 386(10012): 2489–2498. doi:10.1016/S0140-6736(15)00347-5

Vấn đề

- Quan điểm của bạn về giảm/dãn liều thuốc sinh học?
  A. Cần tìm mọi cách để BN giảm/dãn liều thường quy
  B. Giảm/dãn liều tuỳ theo tình trạng hoạt động của bệnh

Drugs
https://doi.org/10.1007/s40265-018-0994-3

REVIEW ARTICLE

CrossMark

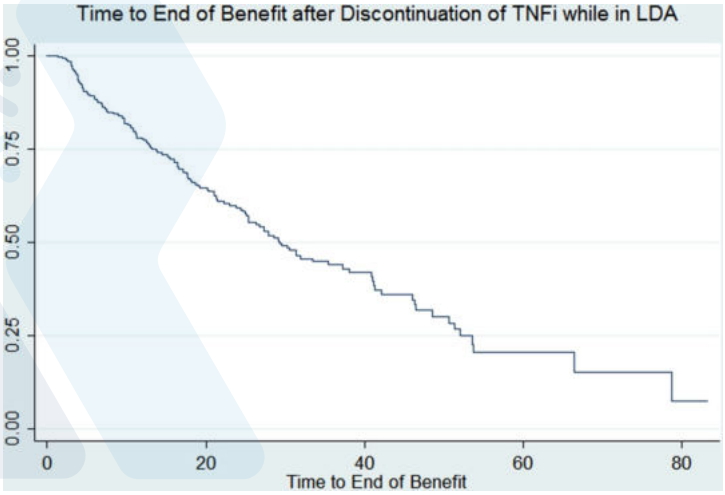
Tapering and Discontinuation of Biologics in Patients with Psoriatic Arthritis with Low Disease Activity

Có thể xem xét giảm/dãn liều ở BN ổn định (chứng cứ rất yếu)
Việc ngưng hẳn thuốc sinh học làm tăng cao nguy cơ mất đáp ứng điều trị
Các yếu tố dự đoán giảm/dãn liều sẽ gây mất đáp ứng: bệnh hoạt tính cao tại thời điểm ngưng thuốc sinh học, hút thuốc lá, nam giới

by studies to define patients eligible for bDMARD tapering or discontinuation and the process by which this occurs. We also review the outcomes of bDMARD tapering and discontinuation, the predictors, and the likelihood of restoring remission following relapse. To date, bDMARD tapering seems to be feasible and safe in patients with PsA who are in remission or with low disease activity. Lower disease activity prior to tapering seems to increase the likelihood of successful bDMARD tapering. In contrast, discontinuing bDMARDs appears to carry a substantial risk of loss of remission. Those with higher disease activity at time of tumour necrosis factor inhibitors discontinuation, current smokers, male sex, increased skin involvement, and synovial hypertrophy seen on ultrasound prior to discontinuation are at greater risk of losing remission post-bDMARD discontinuation. In those who lose remission, reinstating the standard dose of bDMARD appears to be effective in restoring remission.

Ngưng thuốc?

- Quan sát 302 BN trong đoàn hệ CORRONA, ngưng TNFi sau khi đạt LDA kéo dài.
- Tại thời điểm ngưng TNFi, thời gian mắc PsA trung bình là 9.8 năm, CDAI trung bình là 3.9, thời gian dùng TNFi trung bình là 1.5 năm.
- Thời gian trung bình tính từ lúc ngưng thuốc đến lúc mất đáp ứng là 29.2 tháng. Tính đến lần khám cuối cùng, **179 (55.1%) BN vẫn đạt LDA kéo dài.**
- YTNC khiến ngưng TNFi thất bại là bệnh hoạt tính (CDAI≥3.2) và hút thuốc lá.



RMD Open 2017;**3:**e000395. doi: 10.1136/rmdopen-2016-000395

Arthritis & Rheumatology
Vol. 71, No. 1, January 2019, pp 5–32
DOI 10.1002/art.40726

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

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 Reston[20]

Các phương thức điều trị VKVN

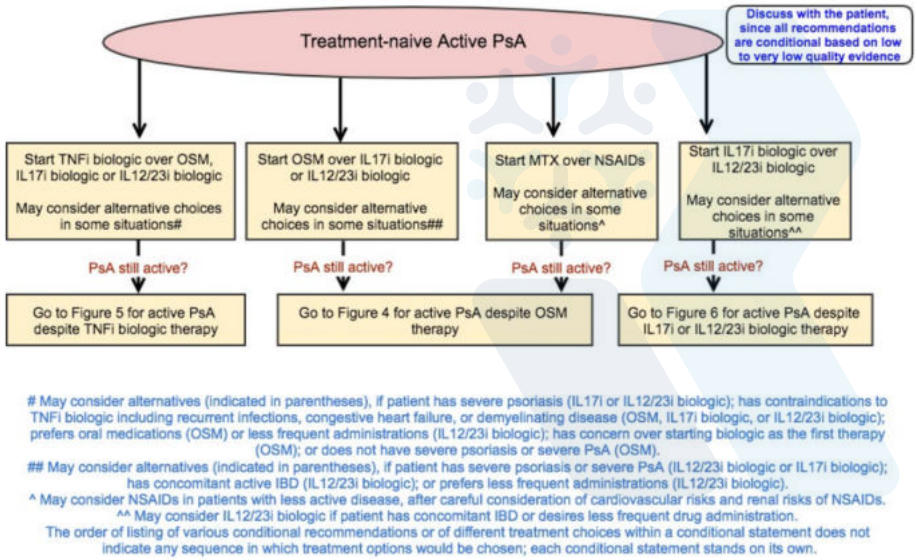
Non-pharmacologic therapies	• physical therapy, occupational therapy, smoking cessation, weight loss, massage therapy, exercise
Symptomatic treatments	• nonsteroidal anti-inflammatory drugs, glucocorticoids, local glucocorticoid injections
OSM	• methotrexate, sulfasalazine, cyclosporine, leflunomide,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

Figure 1. Pharmacologic, nonpharmacologic, and symptomatic therapies for psoriatic arthritis. Pharmacologic therapies are displayed in the blue boxes and include oral small molecules (OSMs), tumor necrosis factor inhibitor (TNFi) biologics, interleukin-17 inhibitor (IL-17i) biologics, an IL-12/23i biologic, CTLA4-immunoglobulin, and a JAK inhibitor. While there are numerous nonpharmacologic therapies available, 6 of these are addressed in this guideline. Symptomatic therapies include nonsteroidal antiinflammatory drugs, systemic glucocorticoids, and local glucocorticoid injections. Systemic glucocorticoids or local injections are not addressed in this guideline.

Arthritis & Rheumatology Vol. 71, No. 1, January 2019, pp 5–32 DOI 10.1002/art.40726

Lựa chọn đầu tiên cho VKVN?

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals



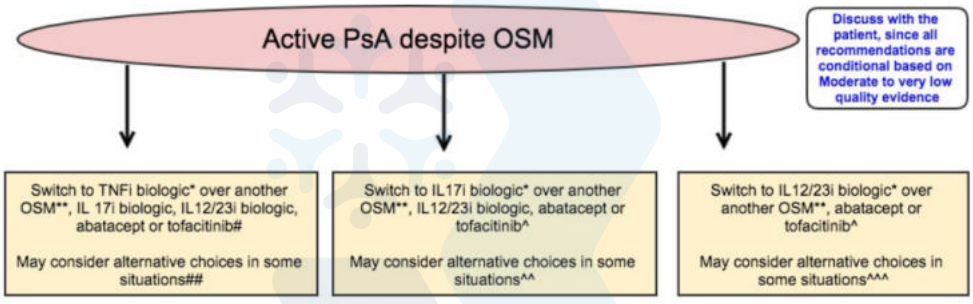
May consider alternatives (indicated in parentheses), if patient has severe psoriasis (IL17i or IL12/23i biologic); has contraindications to TNFi biologic including recurrent infections, congestive heart failure, or demyelinating disease (OSM, IL17i biologic, or IL12/23i biologic); prefers oral medications (OSM) or less frequent administrations (IL12/23i biologic); has concern over starting biologic as the first therapy (OSM); or does not have severe psoriasis or severe PsA (OSM).
May consider alternatives (indicated in parentheses), if patient has severe psoriasis or severe PsA (IL12/23i biologic or IL17i biologic); has concomitant active IBD (IL12/23i biologic); or prefers less frequent administrations (IL12/23i biologic).
^ May consider NSAIDs in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.
^^ May consider IL12/23i biologic if patient has concomitant IBD or desires less frequent drug administration.
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Active PsA was defined as symptoms at **an unacceptably bothersome level as reported by the patient, and judged by the examining health care provider** to be due to PsA based on the presence of at least 1 of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD).

Arthritis & Rheumatology Vol. 71, No. 1, January 2019, pp 5–32 DOI 10.1002/art.40726

Làm gì nếu không đáp ứng csDMARD?

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

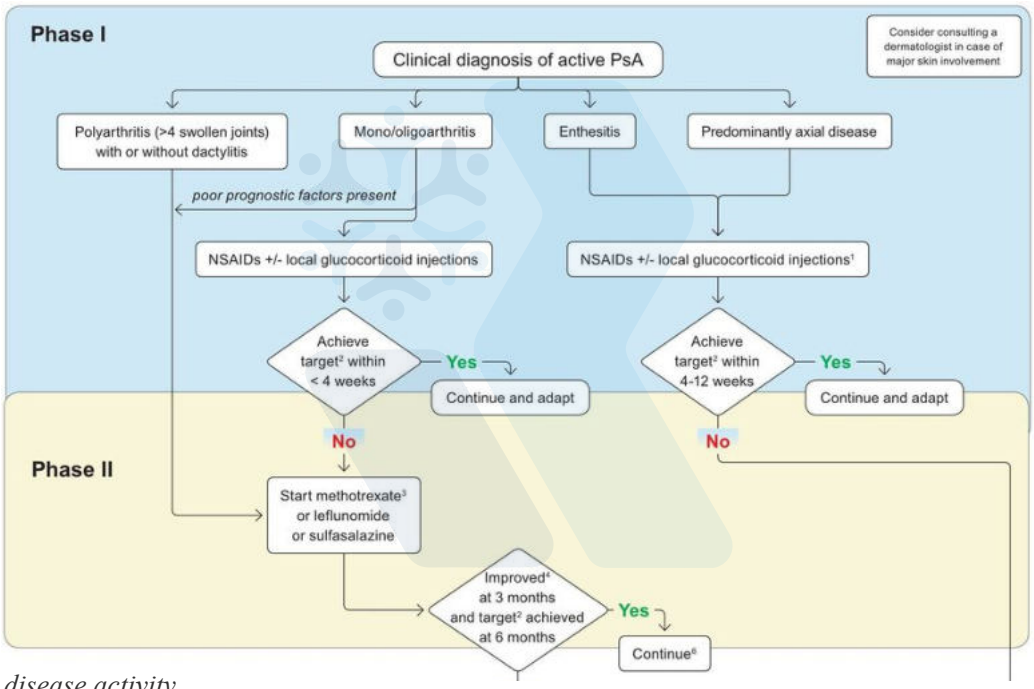


* For each biologic, biologic monotherapy is conditionally recommended over biologic + MTX combination therapy.
** Add apremilast over switching to apremilast; Switch to another OSM (except apremilast) over adding another OSM
# Please see Figure 5 for details and treatment options if patient has active PsA despite TNFi biologic.
^ please see Figure 6 for details and treatment options if patient has active PsA despite IL17i or IL12/23i biologic
May consider alternatives (indicated in parentheses), if patient has severe psoriasis (IL17i or IL12/23i biologic); has contraindications to TNFi including recurrent infections, congestive heart failure, or demyelinating disease (OSM, IL17i biologic, IL12/23i biologic, abatacept or tofacitinib); prefers oral medications (OSM, tofacitinib) or less frequent administrations (IL12/23i biologic).
^^ May consider alternatives (indicated in parentheses), if patient has concomitant active IBD (IL12/23i biologic); absence of severe psoriasis or PsA (OSM); has recurrent serious infections (abatacept); has recurrent candida infections (tofacitinib); prefers oral medications (OSM, tofacitinib) or less frequent administrations (IL12/23i biologic).
^^^ May consider alternatives (indicated in parentheses), if patient has absence of severe psoriasis or severe PsA (OSM); has recurrent or serious infections (abatacept); prefers oral medications (OSM, tofacitinib).
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Arthritis & Rheumatology Vol. 71, No. 1, January 2019, pp 5–32 DOI 10.1002/art.40726

Lựa chọn đầu tiên trong VKVN?

eular EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

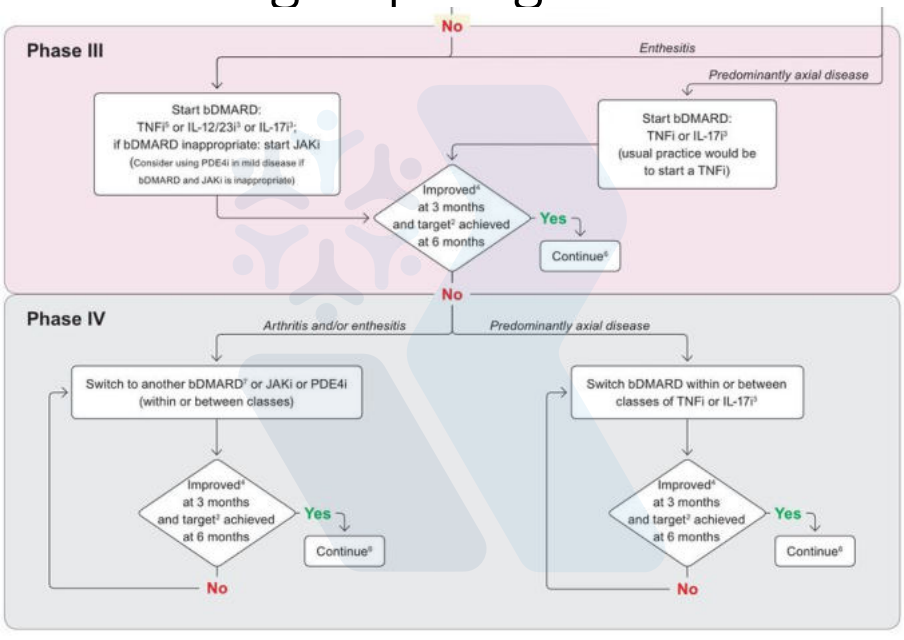


Remission or low disease activity
In PsA DAPSA or MDA should be considered to define the target.

Annals of the Rheumatic Diseases 2020;**79:**700-712.
Annals of the Rheumatic Diseases 2018;**77:**3-17.

Làm gì nếu không đáp ứng csDMARD?

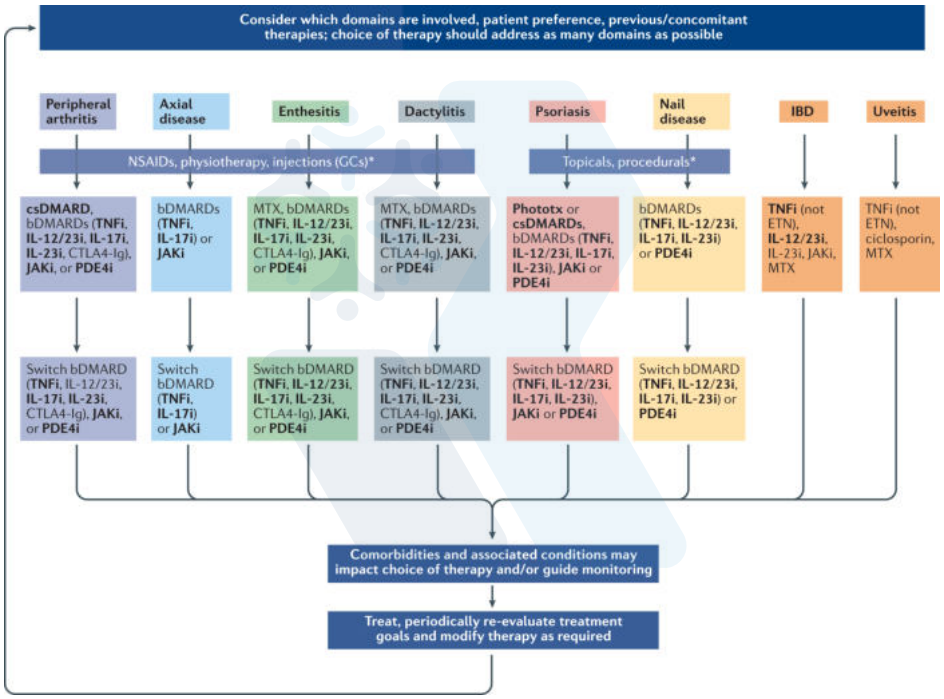
eular EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY



1. No glucocorticoids for axial disease.
2. The target is remission or low disease activity (especially with long standing disease) in accordance with the treat-to-target recommendations.
3. Preferred in the presence of relevant skin involvement, however in case of concomitant inflammatory bowel disease or uveitis, an anti-TNF antibody would be preferred.
4. Improvement means at least 50% reduction in disease activity.
5. As add-on to methotrexate.
6. Consider cautious tapering in sustained remission.
7. Including abatacept.
8. For definition of individual items see text. Phase I: recommendations 1, 2, 3, 4, 5; Phase II: recommendations 1, 3, 4, 5, 12; Phase III: recommendations 6, 8, 9, 10, 12; Phase IV: recommendations 7, 11,12.

Annals of the Rheumatic Diseases 2020;**79:**700-712.

GRAPPA 2021



Nature Reviews Rheumatology **volume 18**, pages465–479 (2022)

Kết luận

- Nhóm ức chế TNF là nhóm thuốc có nhiều dữ liệu nhất về tính an toàn và hiệu quả trong điều trị VKVN.
- Ngày càng có nhiều dữ liệu ủng hộ việc sử dụng sớm thuốc sinh học trong điều trị VKVN.
- Việc điều trị cần cân nhắc toàn diện các biểu hiện tại khớp, ngoài khớp, và bệnh kèm theo.
- Điều trị theo mục tiêu sẽ giúp đạt hiệu quả tốt hơn.
- Việc giảm/dãn liều không nên đặt ra thường quy, cần cân nhắc và bàn bạc với BN trước khi giảm/dãn liều.