Revista Argentina de
REUMATOLOGÍA
Sociedad Argentina de Reumatología

CAPÍTULO 2: Manejo terapéutico en pacientes con artritis reumatoidea

CHAPTER 2: Therapeutic management in patients with rheumatoid arthritis

Palabras clave: tratamiento; manejo terapéutico; artritis reumatoidea.

Key words: *treatment; therapeutic management; rheumatoid arthritis.*

Revista Argentina de Reumatología 2025; Vol. 36 (8-22)

INTRODUCCIÓN

En este apartado se presentan las 21 recomendaciones sobre el tratamiento de pacientes con artritis reumatoidea (AR) que responden a las 71 preguntas PICO (*Patient, Intervention, Comparison, Outcome*). La mayoría se analizó en forma cuantitativa a través de la metodología GRADE (*Sistem Grade of Recommendation, Assessment, Development, and Evaluation*). Toda evidencia que no pudo examinarse por GRADE se analizó en forma cualitativa (Material suplementario-apéndice 1-3).

RECOMENDACIONES

1. **Se recomienda dieta mediterránea en los pacientes con AR**
   Calidad de la evidencia: baja.
   Fuerza de la recomendación: **débil a favor**.
   Votación: 81%.

   La evidencia es baja y cualitativa, con 5 estudios prospectivos[1-5] y un estudio transversal[6] del Hospital Escuela Eva Perón Granadero Baigorria de Santa Fe, Argentina, que muestran algunos resultados significativos a favor de la dieta mediterránea.

2. **Se recomienda metotrexato (MTX) subcutáneo (SC) sobre vía oral (VO) en los pacientes con AR**
   Calidad de la evidencia: baja.
   Fuerza de la recomendación: **débil a favor**.
   Votación: 87%.

3. **Se recomienda MTX SC sobre VO en dosis ≥15 mg/SC semanal en los pacientes con AR**
   Calidad de la evidencia: baja.
   Fuerza de la recomendación: **fuerte a favor**.
   Votación: 94% (2° votación).

   Con respecto al MTX, se revisaron 4 estudios prospectivos y uno retrospectivo y, si bien el nivel de evidencia fue bajo, todos comprobaron que el MTX SC fue más efectivo que el MTX VO[7-10]. Cuando la dosis de MTX es ≥15 mg/semana, recomendamos en forma fuerte administrarlo por vía SC ya que la evidencia demuestra mayor efectividad, probablemente vinculada a una mayor biodisponibilidad[7,9-11].

4. **En pacientes con AR activa con respuesta inadecuada (RI) a drogas antirreumáticas modificadoras de la enfermedad (DMARD) sintéticos convencionales (-sc) se recomienda avanzar tratamiento con un DMARD biológico (-b).**
   Calidad de la evidencia: baja a moderada para infliximab (IFX) y abatacept (ABA) y moderada a alta para el resto de los DMARD-b.
   Fuerza de la recomendación: **fuerte a favor**.
   Votación: 100%.

La votación de los expertos fue fuerte a favor en forma unánime dado que a través de todos los estudios analizados la eficacia de los DMARD-b fue superior con respecto a los DMARD-sc y la seguridad fue similar[12-62].

5. **En pacientes con AR activa con RI a DMARD-sc se recomienda avanzar tratamiento con un DMARD sintético dirigido (-sd)**
   Calidad de la evidencia: moderada a alta.
   Fuerza de la recomendación: fuerte a favor.
   Votación: 87%.

Con una calidad de evidencia y resultados similares, en caso de falla a DMARD-sc, también se recomienda avanzar el tratamiento a un inhibidor de la Janus quinasa (JAKi)[63-82], aunque el porcentaje de votación bajó a 87%. Claramente esto se debe a las cuestiones de seguridad, por lo cual, ante la indicación de un JAKi, se recomienda precaución en pacientes ≥65 años, tabaquistas actuales o pasados, con historia de enfermedad cardiovascular (CV) aterosclerótica u otros factores de riesgo CV, con factores de riesgo para malignidades y/o con factores de riesgo para eventos tromboembólicos (VTE).

6. **En pacientes con AR activa, DMARD-sc *naïve*, no se recomienda inicio de tratamiento con DMARD-b/-sd**
   Calidad de la evidencia: moderada a alta.
   Fuerza de la recomendación: débil en contra (sobre la recomendación de iniciar tratamiento en pacientes con AR DMARD-sc *naïve* con DMARD-b/-sd).
   Votación: 88-100% (2° votación).

Los diferentes estudios evaluados muestran evidencia cuantitativa con eficacia superior de los DMARD-b/-sd versus los DMARD-sc y seguridad similar[83-103], a excepción de IFX debido a una mayor frecuencia de infecciones serias y más discontinuaciones por eventos adversos (EA)[104-109], y de tocilizumab (TCZ) en el que algunos de los estudios mostraron mayor frecuencia de EA en TCZ + DMARD-sc respecto de los DMARD-sc[110-114]. A pesar de estos resultados, recomendamos comenzar el tratamiento con un DMARD-sc, y en caso que el paciente no responda, escalar el tratamiento. Sin embargo, debemos tener en cuenta que la votación fue débil, ya que consideramos que ante determinadas situaciones particulares, como intolerancia o contraindicación para DMARD-sc, se podría comenzar con un DMARD-b o un DMARD-sd.

7. **No se recomienda monoterapia con ciertos DMARD-b como inhibidores del factor de necrosis tumoral (TNFi), rituximab (RTX) y ABA**
   Calidad de la evidencia: muy baja para IFX, baja a moderada para etanercept (ETN) y adalimumab (ADA), moderada para ABA y RTX, y moderada a alta para golimumab (GLM) y certolizumab pegol (CZP).
   Fuerza de la recomendación: débil en contra (sobre la recomendación de monoterapia con TNFi, RTX y ABA).
   Votación: 82-100% (2° votación).

La evidencia científica muestra que en términos generales la eficacia y la seguridad de estos DMARD-b en monoterapia son similares a los DMARD-sc[56-61,84, 93-95,115-130]. Sin embargo, la fuerza de esta recomendación fue débil porque hay cierta data de ETN[117], GLM[127], CZP[128-130] y RTX[56,61] con eficacia superior en monoterapia en algunos desenlaces, de ADA con mejor desenlace radiográfico[84] y de ABA en monoterapia a través del estudio ACCOMPANY[131].

8. **Se recomienda monoterapia con otros DMARD-b como inhibidores de la interleuquina 6 (IL-6i) y JAKi**
   Calidad de la evidencia: moderada a alta.
   Fuerza de la recomendación: fuerte a favor.
   Votación: 93-94% (2° votación).

La mayoría de los estudios evaluados, tanto en pacientes DMARD-sc *naïve* como con falla previa a DMARD-sc, muestra una eficacia comparable de los IL-6i y JAKi en monoterapia versus estos agentes combinados con MTX u otros DMARD-sc[64,102,103,110-112,132-146]. En general, también presentan una seguridad similar[64,102,103,110-112,132-146]. Sin embargo, hubo tendencia hacia tasas más bajas de elevaciones de las enzimas hepáticas con TCZ monoterapia en comparación con TCZ + MTX[110,111,134].

9. **En pacientes con AR activa, con RI DMARD-sc, se recomienda el uso de DMARD-b/-sd ante el uso de DMARD-sc en forma combinada**
   Calidad de la evidencia: moderada.
   Fuerza de la recomendación: fuerte a favor.
   Votación: 76-93%.

Todos los estudios muestran eficacia superior y seguridad superior con el uso de DMARD-b/-sd en pacientes con AR activa y RI DMARD-sc, en

comparación con el tratamiento con DMARD-sc en forma combinada[17,109,147-155]. De todas maneras, los expertos consideramos que se puede indicar tratamiento combinado con DMARD-sc en casos de pacientes activos con demora en acceder al tratamiento solicitado.

10. En pacientes con AR activa, con RI a un DMARD-b/-sd, se recomienda preferentemente el uso de otro DMARD-b/-sd con diferente mecanismo de acción
Calidad de la evidencia: moderada a alta.
Fuerza de la recomendación: débil a favor.
Votación: 95-100%.

Existe una vasta cantidad de estudios que, ante la falla a un DMARD-b, avala tanto el cambio del tratamiento por un agente con diferente mecanismo de acción como cambiar por un agente con el mismo mecanismo de acción[82,156-176]. El estudio ROC muestra que ante la falla a un 1° TNFi, el cambio por un agente no TNFi fue más efectivo[169], aunque también hay evidencia del estudio GO AFTER de buena respuesta de GLM ante la falla a TNFi[156]. Sin embargo, los expertos aconsejamos en forma débil el cambio de mecanismo de acción.

11. En pacientes con AR activa no se recomienda preferentemente el tratamiento con un TNFi en especial + DMARD-sc versus otro TNFi + DMARD-sc
Calidad de la evidencia: moderada a alta.
Fuerza de la recomendación: fuerte en contra (sobre la recomendación de preferir un TNFi ante otro TNFi).
Votación: 95% (2° votación).

Esta recomendación se apoya fundamentalmente en el estudio cabeza-cabeza EXXELERATE que muestra eficacia y seguridad similar entre CZP + DMARD-sc versus ADA + DMARD-sc[177]. A pesar de que consideramos que algunos TNFi tienen algunas características distintivas como, por ejemplo, los agentes monoclonales tienen mayor riesgo para tuberculosis (TBC)[178] y el CZP posee un nivel de evidencia más alto en el embarazo y la lactancia, etc.[179,180].

12. En pacientes con AR activa se recomienda en forma débil ABA + DMARD-sc ante TNFi + DMARD-sc
Calidad de la evidencia: moderada.
Fuerza de la recomendación: débil a favor.
Votación: 76% (2° votación).

Esta recomendación se basa fundamentalmente en los resultados de los estudios cabeza-cabeza AMPLE, EARLY AMPLE y ATTEST, que demostraron una seguridad superior para ABA en EA, EA serios, infecciones serias, discontinuaciones por EA y reacciones en el sitio de la inyección en comparación con ADA e IFX. Y una mayor eficacia en ciertos desenlaces en pacientes seropositivos para anticuerpos contra péptidos citrulinados (ACPA) y aquellos que poseen epítopo compartido (EC)[50,181-184]. Sin embargo, recientemente el estudio AMPLIFIED no mostró diferencias en la eficacia entre estos dos DMARD-b en pacientes con AR temprana, seropositivos y epítopo compartido positivo[185].

13. En pacientes con AR activa se recomienda preferentemente IL-6i monoterapia ante ADA monoterapia
Calidad de la evidencia: moderada a alta.
Fuerza de la recomendación: fuerte a favor.
Votación: 100%.

Esta recomendación se fundamenta en la mayor eficacia de TCZ en monoterapia versus ADA en monoterapia que fue ratificada a través de los estudios cabeza-cabeza ADACTA y MONARCH[186-188].

14. En pacientes con AR activa se recomienda preferentemente ETN + DMARD-sc ante TCZ + DMARD-sc
Calidad de la evidencia: moderada a alta.
Fuerza de la recomendación: débil a favor.
Votación: 89% (2° votación).

Los expertos argumentaron esta recomendación fundamentalmente en el estudio ENTRACTE que, si bien mostró una seguridad CV similar en ambas drogas, TCZ tuvo seguridad inferior con mayor frecuencia de infecciones serias y perforación gastrointestinal (GI)[189].

15. En pacientes con AR activa con falla a un DMARD-sc no se recomienda JAKi ante un DMARD-b
Calidad de la evidencia: moderada a alta.
Fuerza de la recomendación: débil en contra (sobre la recomendación de indicar un JAKi ante un DMARD-b).
Votación: 100% (2° votación).

La fuerza de esta recomendación fue débil porque aunque la eficacia para JAKi fue superior en la mayoría de los estudios cabeza-cabeza, la

magnitud de esa diferencia en desenlaces estrictos, como remisión booleana o por *simpliflied disease activity index* (SDAI), no fue tan importante[68,141,190-196], y por otro lado, ADA como agente comparador presentó más discontinuaciones por EA y EA serios en comparación con baricitinib (BAR)[196]. No podemos dejar de considerar la evidencia posterior de seguridad a través del estudio *Oral Surveillance*, que demostró mayor incidencia de EA CV, infecciosos y neoplásicos de tofacitinib (TOF) versus TNFi, especialmente en la población ≥65 años[197]. Sin existir hasta el momento otros estudios similares con los otros JAKi y dado que tienen un mecanismo de acción semejante, la mayoría de las agencias regulatorias y recomendaciones del tratamiento en el mundo ha extrapolado estos datos de seguridad de TOF a los demás JAKi.

16. En pacientes con AR y enfermedad pulmonar intersticial (EPI) concomitante se recomienda el tratamiento con MTX, ABA y RTX fuerte a favor, y con TNFi, TCZ, JAKi y LFN débil a favor

Un relativo bajo número de estudios se incluyó en la revisión y la calidad de la evidencia fue de moderada a muy baja, motivo por el cual se realizó un análisis cualitativo[198-222]. A continuación, se describe el número de estudios analizados, la calidad de la evidencia, la fuerza de la recomendación y el porcentaje de votación a través de una tabla.

Droga	N° de estudios analizados	Calidad de la evidencia	Fuerza de la recomendación	Votación
MTX	3 estudios observacionales, 1 estudio retrospectivo	Baja a moderada	**Fuerte a favor**	72%
LFN	2 estudios retrospectivos	Muy baja	**Débil a favor**	100% (2°)
TNFi	5 estudios observacionales	Baja	**Débil a favor**	94% (2°)
ABA	1 estudio prospectivo, 2 estudios observacionales, 4 estudios retrospectivos	Baja	**Fuerte a favor**	88%
RTX	2 estudios observacionales, 3 estudios retrospectivos	Baja a moderada	**Fuerte a favor**	84%
TCZ	2 estudios observacionales	Muy baja a baja	**Débil a favor**	88%
JAKi	1 estudio retrospectivo	Muy baja	**Débil a favor**	80% (2°)

MTX: metotrexato; LFN: leflunomida; i: inhibidor; TNF: factor de necrosis tumoral; ABA: abatacept; RTX: rituximab; TCZ: tocilizumab; JAK: Janus quinasa.

17. En pacientes con AR y EPI con fibrosis progresiva se recomienda tratamiento con nintedanib (NIN) fuerte a favor y con pirfenidona (PIR) débil a favor
Calidad de la evidencia: baja.
Fuerza de la recomendación: NIN fuerte a favor / PIR débil a favor.
Votación: NIN 100% / PIR 100% (2° votación).

La evidencia sobre NIN se analizó en forma cualitativa, incluyendo un análisis de subgrupo de un ensayo clínico y dos estudios *post-hoc* de dos ensayos clínicos. Los datos sugieren que NIN tiene un efecto clínicamente significativo en la desaceleración de la progresión de la enfermedad pulmonar en pacientes con EPI progresiva relacionada con enfermedades autoinmunes fibrosantes, mostrando una reducción de la tasa de disminución de la capacidad vital forzada (CVF) en pacientes con un patrón fibrótico[223-225]. La PIR cuenta con un ERC, pero el mismo finalizó tempranamente por falta de potencia estadística, por este motivo, no cumplió con el criterio de valoración principal. Sin embargo, la PIR redujo la tasa de disminución de la CVF a lo largo del tiempo en pacientes con EPI asociada a AR[226].

18. En pacientes con AR y vasculitis reumatoidea activa se recomienda el tratamiento con RTX o con ABA
Calidad de la evidencia: baja.
Fuerza de la recomendación: fuerte a favor.
Votación: 74% (2° votación).

La evidencia es baja: dos estudios observacionales en RTX y solo a través de reporte de casos en ABA[227-229].

19. En pacientes con AR en remisión sostenida se recomienda espaciado/disminución de dosis de DMARD-b o DMARD-sd versus suspensión de los mismos
Calidad de la evidencia: baja a moderada.

Fuerza de la recomendación: DMARD-b fuerte a favor / DMARD-sd débil a favor. Votación: 90%.

Para esta pregunta PICO se evaluaron de forma cuantitativa 9 estudios prospectivos y un estudio transversal, y reportaron mejores respuestas y desenlaces de eficacia en pacientes que disminuyeron o aumentaron intervalos de dosis de DMARD-b en comparación con aquellos que suspendieron el tratamiento, con un perfil de seguridad comparable[93,85,230-236]. No encontramos la misma calidad de evidencia con DMARD-sd; sin embargo, decidimos extrapolar la recomendación como opinión de expertos con una recomendación débil a favor.

20. En pacientes con AR en remisión sostenida se recomienda espaciado/disminución de la dosis de DMARD-b o DMARD-sd versus continuación débil a favor
Calidad de la evidencia: moderada a alta.
Fuerza de la recomendación: débil a favor.
Votación: 100% (2° votación).

Se analizaron 15 estudios. La síntesis cuantitativa de los mismos evidenció que la disminución de la dosis o el aumento del intervalo de DMARD-b fue similar a la continuación en la mayoría de los desenlaces de eficacia o cantidad de brotes con un perfil de seguridad comparable. De todas formas, los expertos respaldamos la intervención de disminuir dosis o ampliar los intervalos de dosis, tanto de DMARD-b como -sd, en pacientes en remisión sostenida ya sea para bajar la incidencia de EA o para disminuir los costos[95,230,231,233-244].

21. En pacientes con AR en remisión sostenida se recomienda primero el espaciado/disminución de dosis de DMARD-b o DMARD-sd versus el espaciado/disminución de la dosis de DMARD-sc
Calidad de la evidencia: moderada a alta.
Fuerza de la recomendación: débil a favor.
Votación: 90% (2° votación).

Si bien se analizaron 3 estudios[245-247], esta recomendación se basa fundamentalmente en el estudio TARA en el cual no hubo diferencias en las tasas de brote entre la disminución de dosis de TNFi versus de DMARD-sc de modo que, a efectos similares, los argumentos sobre costos nos inclinan a recomendar reducir primero los DMARD-b/-sd[247].

BIBLIOGRAFÍA

1. Araújo CA, Moraes-Fontes MF, Santos L, Riso N, et al. Omega-3 fatty acids and Mediterranean diet as complimentary therapies for rheumatoid arthritis. Arthritis Rheum. 2014;66:S1050.
2. García-Morales JM, Lozada-Mellado M, Hinojosa-Azaola A, Llorente L, Ogata-Medel M, Pineda-Juárez JA, et al. Effect of a dynamic exercise program in combination with Mediterranean diet on quality of life in women with rheumatoid arthritis. J Clinical Rheumatol. 2020;26(7 Suppl 2):S116-22.
3. Sadeghi A, Tabatabaiee M, Mousavi MA, Mousavi SN, Abdollahi Sabet S, Jalili N. Dietary pattern or weight loss: which one is more important to reduce disease activity score in patients with rheumatoid arthritis? A randomized feeding trial. Int J Clin Pract. 2022;2022:6004916.
4. Sköldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. Ann Rheumatic Dis. 2003;62(3):208-14.
5. McKellar G, Morrison E, McEntegart A, Hampson R, Tierney A, Mackle G, et al. A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis living in areas of social deprivation in Glasgow. Ann Rheum Diseases. 2007;66(9):1239-43.
6. Satler ME, Conte M, Raogio JO, Berbotto GA. Relación entre el consumo dietético de pescados ricos en ácidos grasos pacientes con artritis reumatoidea. Rev Arg Reumatol. 2014;25(4Supl)#124.
7. Braun J, Kästner P, Flaxenberg P, Währisch J, Hanke P, Demary W, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008;58(1):73-81.
8. Islam MS, Haq SA, Islam MN, Azad AK, Islam MA, Barua R, et al. Comparative efficacy of subcutaneous versus oral methotrexate in active rheumatoid arthritis. Mymensingh Med J. 2013;22(3):483-8.
9. Scott DG, Claydon P, Ellis C. Retrospective evaluation of continuation rates following a switch to subcutaneous methotrexate in rheumatoid arthritis patients failing to respond to or tolerate oral methotrexate: the MENTOR study. MENTOR study. Scand J Rheumatol. 2014;43(6):470-6.
10. Hazlewood GS, Thorne JC, Pope JE, Lin D, Tin D, Boire G, et al. The comparative effectiveness of oral versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis. Ann Rheum Dis. 2016;75(6):1003-8.
11. Gottheil S, Thorne JC, Schieir O, Boire G, Haraoui B, Hitchon C, et al. Early use of subcutaneous MTX monotherapy vs. MTX oral or combination therapy significantly delays time to initiating biologics in early RA. Arthritis and Rheumatology. Conference: ACR/ARHP 2016. United states. et al. Conference start: 20161111. 2016;68:4208-10.
12. Kim J, Ryu H, Yoo DH, Park SH, Song GG, Park W, et al. A clinical trial and extension study of infliximab in Korean patients with active rheumatoid arthritis despite methotrexate treatment. J Korean Med Sci. 2013;28(12):1716-22.
13. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354(9194):1932-9.

14. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000;343(22):1594-602.
15. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006;54(4):1075-86.
16. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004;50(4):1051-65.
17. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006;54(4):1063-74.
18. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004;363(9410):675-81.
19. Hobbs K, Deodhar A, Wang B, Bitman B, Nussbaum J, Chung J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etanercept in patients with moderately active rheumatoid arthritis despite DMARD therapy. Springerplus. 2015;4:113.
20. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003;30(12):2563-71.
21. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50(5):1400-11.
22. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48(1):35-45.
23. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009;68(6):789-96.
24. Li Z, Zhang F, Kay J, Fei K, Han C, Zhuang Y, et al. Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy. Int J Rheum Dis. 2016;19(11):1143-56.
25. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis. 2012;71(6):817-24.
26. Weinblatt ME, Bingham CO, Mendelsohn AM, Kim L, Mack M, Lu J, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Ann Rheum Dis. 2013;72(3):381-9.
27. Conaghan PG, Emery P, Østergaard M, Keystone EC, Genovese MC, Hsia EC, et al. Assessment by MRI of inflammation and damage in rheumatoid arthritis patients with methotrexate inadequate response receiving golimumab: results of the GO-FORWARD trial. Ann Rheum Dis. 2011;70(11):1968-74.
28. Genovese MC, Han C, Keystone EC, Hsia EC, Buchanan J, Gathany T, et al. Effect of golimumab on patient-reported outcomes in rheumatoid arthritis: results from the GO-FORWARD study. J Rheumatol. 2012;39(6):1185-91.
29. Bingham CO, Weinblatt M, Han C, Gathany TA, Kim L, Lo KH, et al. The effect of intravenous golimumab on health-related quality of life in rheumatoid arthritis: 24-week results of the phase III GO-FURTHER trial. J Rheumatol. 2014;41(6):1067-76.
30. Schiff MH, von Kempis J, Goldblum R, Tesser JR, Mueller RB. Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase. Ann Rheum Dis. 2014;73(12):2174-7.
31. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(5):715-24.
32. Bi L, Li Y, He L, Xu H, Jiang Z, Wang Y, et al. Efficacy and safety of certolizumab pegol in combination with methotrexate in methotrexate-inadequate responder Chinese patients with active rheumatoid arthritis: 24-week results from a randomised, double-blind, placebo-controlled phase 3 study. Clin Exp Rheumatol. 2019;37(2):227-34.
33. Kang YM, Park YE, Park W, Choe JY, Cho CS, Shim SC, et al. Rapid onset of efficacy predicts response to therapy with certolizumab plus methotrexate in patients with active rheumatoid arthritis. J Korean Med Sci. 2018;33(6):1224-33.
34. Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009;68(6):797-804.
35. Keystone E, van der Heijde D, Mason D, Jr., Landewé R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008;58(11):3319-29.
36. Choy E, McKenna F, Vencovsky J, Valente R, Goel N, Vanlunen B, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. Rheumatology (Oxford). 2012;51(7):1226-34.

37. Kivitz A, Olech E, Borofsky M, Zazueta BM, Navarro-Sarabia F, Radominski SC, et al. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis Care Res. 2014;66(11):1653-61.

38. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987-97.

39. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968-80.

40. Baek HJ, Lim MJ, Park W, Park SH, Shim SC, Yoo DH, et al. Efficacy and safety of tocilizumab in Korean patients with active rheumatoid arthritis. J Korean Med Sci. 2019;34(4):917-31.

41. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011;63(3):609-21.

42. Tanaka Y, Wada K, Takahashi Y, Hagino O, van Hoogstraten H, Graham NMH, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a randomized, placebo-controlled phase III trial in Japan. Arthritis Res Ther. 2019;21(1):79.

43. Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate. Results of a phase III study. Arthritis Rheumatol. 2015;67(6):1424-37.

44. Genovese MC, Stanislav M, Van Hoogstraten H, Martincova R, Fan C, Van Adelsberg J. Efficacy of sarilumab plus methotrexate in achieving clinical remission, using 4 different definitions, in patients with active, moderate-to-severe rheumatoid arthritis in a phase 3 study. Arthritis Rheumatol. 2015;67(Suppl 10):#2770.

45. Strand V, Kosinski M, Chen CI, Joseph G, Rendas-Baum R, Graham NMH, et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. Arthritis Res Ther. 2016;18(1):198.

46. Genovese MC, van Adelsberg J, Fan C, Graham NMH, van Hoogstraten H, Parrino J, et al. Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: safety, efficacy and radiographic outcomes. Rheumatology (Oxford). 2018;57(8):1423-31.

47. Matsubara T, Inoue H, Nakajima T, Tanimura K, Sagawa A, Sato Y, et al. Abatacept in combination with methotrexate in Japanese biologic-naive patients with active rheumatoid arthritis: a randomised placebo-controlled phase IV study. RMD Open. 2018;4(2):e000813.

48. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med. 2003;349(20):1907-15.

49. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144(12):865-76.

50. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67(8):1096-103.

51. Takeuchi T, Matsubara T, Nitobe T, Suematsu E, Ohta S, Honjo S, et al. Phase II dose-response study of abatacept in Japanese patients with active rheumatoid arthritis with an inadequate response to methotrexate. Mod Rheumatol. 2013;23(2):226-35.

52. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006;54(9):2807-16.

53. Emery P, Kosinski M, Li T, Martin M, Williams GR, Becker JC, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol. 2006;33(4):681-9.

54. Russell AS, Wallenstein GV, Li T, Martin MC, Maclean R, Blaisdell B, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. Ann Rheum Dis. 2007;66(2):189-94.

55. Genovese MC, Covarrubias A, Leon G, Mysler E, Keiserman M, Valente R, et al. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis Rheumatol. 2011;63(10):2854-64.

56. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350(25):2572-81.

57. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006;54(5):1390-400.

58. Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE). Ann Rheum Dis. 2010;69(9):1629-35.

59. Peterfy C, Emery P, Tak PP, Østergaard M, DiCarlo J, Otsa K, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. Ann Rheum Dis. 2016;75(1):170-7.

60. Mease PJ, Revicki DA, Szechinski J, Greenwald M, Kivitz A, Barile-Fabris L, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol. 2008;35(1):20-30.

61. Strand V, Balbir-Gurman A, Pavelka K, Emery P, Li N, Yin M, et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. Rheumatology (Oxford). 2006;45(12):1505-13.

62. Behrens F, Koehm M, Rossmanith T, Alten R, Aringer M, Backhaus M, et al. Rituximab plus leflunomide in rheumatoid arthritis: a randomized, placebo-controlled, investigator-initiated clinical trial (AMARA study). Rheumatology (Oxford). 2021;60(11):5318-28.

63. Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum. 2009;60(7):1895-905.

64. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507.

65. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum. 2012;64(4):970-81.

66. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Int Med. 2013;159(4):253-61.

67. Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken). 2011;63(8):1150-8.

68. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García-Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.

69. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013;65(3):559-70.

70. Strand V, Kremer JM, Gruben D, Krishnaswami S, Zwillich SH, Wallenstein GV. Tofacitinib in combination with conventional disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis. Patient-reported outcomes from a phase III randomized Controlled Trial. Arthritis Care Res. 2017;69(4):592-8.

71. Coombs JH, Bloom BJ, Breedveld FC, Fletcher MP, Gruben D, Kremer JM, et al. Improved pain, physical functioning and health status in patients with rheumatoid arthritis treated with CP-690,550, an orally active Janus kinase (JAK) inhibitor: results from a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2010;69(2):413-6.

72. Burmester GR, Kremer JM, Van den Bosch F, Kivitz A, Bessette L, Li Y, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10139):2503-12.

73. Kameda H, Takeuchi T, Yamaoka K, Oribe M, Kawano M, Zhou Y, et al. Efficacy and safety of upadacitinib in Japanese patients with rheumatoid arthritis (SELECT-SUNRISE): a placebo-controlled phase IIb/III study. Rheumatology (Oxford). 2020;59(11):3303-13.

74. Zeng X, Zhao D, Radominski SC, Keiserman M, Lee CK, Meerwein S, et al. Upadacitinib in patients from China, Brazil, and South Korea with rheumatoid arthritis and an inadequate response to conventional therapy. Int J Rheum Dis. 2021;24(12):1530-9.

75. Strand V, Bergman M, Tundia N, Ostor A, Durez P, Song IH, et al. Upadacitinib improves patient-reported outcomes in patients with rheumatoid arthritis and inadequate response to methotrexate: results from select-compare. Ann Rheum Dis. 2019;78:738-9.

76. Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, 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.

77. Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, 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):506-17.

78. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis. 2015;74(2):333-40.

79. Tanaka Y, Lee CK, Li ZG, Li KJ, Ishii T, Won JE, et al. Baricitinib in East Asian patients with active RA and inadequate response to methotrexate: post hoc subanalysis of the RA-BEAM study. Int J Rheum Dis. 2016;19:187-8.

80. Genovese M, Keystone E, Taylor P, Drescher E, Berclaz PY, Lee CH, et al. Results of a blinded Phase2b dose-ranging study of baricitinib in combination with traditional disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Int J Rheum Dis. 2013;16:62.

81. Emery P, Blanco R, Maldonado Cocco J, Chen YC, Gaich CL, Delozier AM, et al. Patient-reported outcomes from a phase III study of baricitinib in patients with conventional synthetic DMARD-refractory rheumatoid arthritis. RMD open. 2017;3(1):e000410.

82. Smolen JS, Kremer JM, Gaich CL, DeLozier AM, Schlichting DE, Xie L, et al. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). Ann Rheum Diseases. 2017;76(4):694-700.

83. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372(9636):375-82.

84. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54(1):26-37.

85. Kavanaugh A, Fleischmann RM, Emery P, Kupper H, Redden L, Guerette B, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. Ann Rheum Dis. 2013;72(1):64-71.

86. Detert J, Bastian H, Listing J, Weiß A, Wassenberg S, Liebhaber A, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. Ann Rheum Dis. 2013;72(6):844-50.

87. Hørslev-Petersen K, Hetland ML, Junker P, Pødenphant J, Ellingsen T, Ahlquist P, et al. Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA Study: an investigator-initiated, randomised, double-blind, parallel-group, placebo-controlled trial. Ann Rheum Dis. 2014;73(4):654-61.

88. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009;60(8):2272-83.

89. Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. Ann Rheum Dis. 2016;75(1):75-83.

90. Emery P, Bingham CO, Burmester GR, Bykerk VP, Furst DE, Mariette X, et al. Certolizumab pegol in combination with dose-optimised methotrexate in DMARD-naïve patients with early, active rheumatoid arthritis with poor prognostic factors: 1-year results from C-EARLY, a randomised, double-blind, placebo-controlled phase III study. Ann Rheum Dis. 2017;76(1):96-104.

91. Hall S, Weinblatt M, Burmester GR, Bykerk V, Furst D, Mariette X, et al. Certolizumab pegol and methotrexate in DMARD-naïve patients with active, severe, rheumatoid arthritis: results from C-EARLY Period 1 including Australian patients. Int J Rheum Dis. 2016;19:170-1.

92. Emery P, Bingham C, Burmester G, Bykerk V, Furst D, Mariette X, et al. Improvements in patient-reported outcomes following 52 weeks of treatment with certolizumab pegol in combination with methotrexate in DMARD-naive patients with severe, active and progressive rheumatoid arthritis: results from the C-early randomized, double-blind, controlled phase 3 study. Value Health. 2015;18(7):A707-A708.

93. Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barre E, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis.2015;74(1):19-26.

94. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis. 2009;68(12):1870-7.

95. Emery P, Tanaka Y, Bykerk V, Bingham C, Huizinga T, Citera G, et al. Patient-reported outcomes of abatacept in combination with MTX in early, MTX-naïve, ACPA positive patients with RA: 1-year results from a phase IIIB study. Arthritis Rheumatol. 2019;71:2493-6.

96. Emery P, Tanaka Y, Bykerk VP, Huizinga TWJ, Citera G, Nys M, et al. Efficacy and safety of abatacept in combination with MTX in early, MTXnaïve, anti-citrullinated protein antibody-positive patients with RA: primary and 1-year results from a phase IIIb study. Arthritis Rheumatol. 2018;70:610-2.

97. Tak PP, Rigby WF, Rubbert-Roth A, Peterfy CG, van Vollenhoven RF, Stohl W, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis. 2011;70(1):39-46.

98. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370(25):2377-86.

99. Fleischmann R, Strand V, Wilkinson B, Kwok K, Bananis E. Relationship between clinical and patient-reported outcomes in a phase 3 trial of tofacitinib or MTX in MTX-naïve patients with rheumatoid arthritis. RMD Open. 2016;2(1):e000232.

100. van Vollenhoven R, Takeuchi T, Pangan A, Friedman A, Chen S, Rischmueller M, et al. Monotherapy with upadacitinib in MTX-naïve patients with rheumatoid arthritis: results at 48 weeks. Arthritis Rheumatol. 2019;71:1609-11.

101. van Vollenhoven R, Takeuchi T, Pangan AL, Friedman A, Mohamed MF, Chen S, et al. A phase 3, randomized, double-blind study comparing upadacitinib monotherapy to MTX monotherapy in MTX-naÏve patients with active rheumatoid arthritis. J Clin Rheumatol. 2019;25(3):S4.

102. Fleischmann R, Takeuchi T, Schlichting DE, Macias WL, Rooney T, Gurbuz S, et al. Baricitinib, methotrexate, or baricitinib plus methotrexate in patients with early rheumatoid arthritis who had received limited or no treatment with disease-modifying anti-rheumatic drugs (DMARDs): phase 3 trial results. Arthritis Rheumatol. 2015;67:(Suppl 10):#1045.

103. Schiff M, Takeuchi T, Fleischmann R, Gaich CL, DeLozier AM, Schlichting D, et al. Patient-reported outcomes of baricitinib in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Res Ther. 2017;19(1):208.

104. Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005;52(1):27-35.

105. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004;50(11):3432-43.

106. Nam JL, Villeneuve E, Hensor EM, Conaghan PG, Keen HI, Buch MH, et al. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). Ann Rheum Dis. 2014;73(1):75-85.

107. Leirisalo-Repo M, Kautiainen H, Laasonen L, Korpela M, Kauppi MJ, Kaipiainen-Seppänen O, et al. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study). Ann Rheum Dis. 2013;72(6):851-7.

108. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2007;146(6):406-15.

109. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005;52(11):3381-90.

110. Bijlsma JWJ, Welsing PMJ, Woodworth TG, Middelink LM, Petho-Schramm A, Bernasconi C, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet. 2016;388(10042):343-55.

111. Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Blanco R, et al. Tocilizumab combination therapy or monotherapy or methotrexate monotherapy in methotrexate-naive patients with early rheumatoid arthritis: 2-year clinical and radiographic results from the randomised, placebo-controlled FUNCTION trial. Ann Rheum Dis. 2017;76(7):1279-84.

112. Teitsma XM, Jacobs JWG, Welsing PMJ, Pethö-Schramm A, Borm MEA, Hendriks L, et al. Patient-reported outcomes in newly diagnosed early rheumatoid arthritis patients treated to target with a tocilizumab- or methotrexate-based strategy. Rheumatology (Oxford). 2017;56(12):2179-89.

113. Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Kelman A, et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis. 2016;75(6):1081-91.

114. Teitsma XM, Jacobs JWG, Welsing PMJ, Pethö-Schramm A, Borm MEA, van Laar JM, et al. Radiographic joint damage in early rheumatoid arthritis patients: comparing tocilizumab- and methotrexate-based treat-to-target strategies. Rheumatology (Oxford). 2018;57(2):309-17.

115. Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology (Oxford). 2005;44(2):157-63.

116. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.

117. Hyrich KL, Symmons DP, Watson KD, Silman AJ. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006;54(6):1786-94.

118. Spertino J, López-Ferrer A, Vilarrasa E, Puig L. Long-term study of infliximab for psoriasis in daily practice: drug survival depends on combined treatment, obesity and infusion reactions. J Eur Acad Dermatol Venereol. 2014;28(11):1514-21.

119. Hobbs K, Chung J, Bitman B, Wang B, Nussbaum J, Collier DH. Efficacy and safety of etanercept (ETN) in patients with moderately active rheumatoid arthritis (RA) despite disease-modifying antirheumatic drug (DMARD) therapy. Ann Rheum Dis. 2014;73.

120. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000;343(22):1586-93.

121. Takeuchi T, Miyasaka N, Zang C, Alvarez D, Fletcher T, Wajdula J, et al. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. Mod Rheumatol. 2013;23(4):623-33.

122. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002;46(6):1443-50.

123. Kameda H, Ueki Y, Saito K, Nagaoka S, Hidaka T, Atsumi T, et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. Mod Rheumatol. 2010;20(6):531-8.

124. van Riel PL, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis. 2006;65(11):1478-83.

125. Keystone EC, Pope JE, Carter Thorne J, Poulin-Costello M, Phan-Chronis K, Vieira A, et al. Two-year radiographic and clinical outcomes from the Canadian methotrexate and etanercept outcome study in patients with rheumatoid arthritis. Rheumatology (Oxford).2016;55(2):327-34.

126. Kameda H, Kanbe K, Sato E, Ueki Y, Saito K, Nagaoka S, et al. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. J Rheumat. 2011;38(8):1585-92.

127. Takeuchi T, Harigai M, Tanaka Y, Yamanaka H, Ishiguro N, Yamamoto K, et al. Golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior treatment with disease-modifying antirheumatic drugs: results of the phase 2/3, multicentre, randomised, double-blind, placebo-controlled GO-MONO study through 24 weeks. Ann Rheum Dis. 2013;72(9):1488-95.

128. Weinblatt ME, Fleischmann R, van Vollenhoven RF, Emery P, Huizinga TW, Cutolo M, et al. Twenty-eight-week results from the REALISTIC phase IIIb randomized trial: efficacy, safety and predictability of response to certolizumab pegol in a diverse rheumatoid arthritis population. Arthritis Res Ther. 2015;17:325.

129. Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009;68(6):805-11.

130. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(4):552-60.

131. Nash P, Nayiager S, Genovese MC, Kivitz AJ, Oelke K, Ludivico C, et al. Immunogenicity, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: results from a phase III, international, multicenter, parallel-arm, open-label study. Arthritis Care Res (Hoboken). 2013;65(5):718-28.

132. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12-9.

133. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66(9):1162-7.

134. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010;69(1):88-96.

135. Durez P, Depresseux G, Nzeusseu Toukap A, Lauwerys B, Meric De Bellefon L, Stoenoiu M, et al. Rate of remission by tocilizumab or methotrexate induction therapy in early active rheumatoid arthritis: results of the tomera trial. Ann Rheum Dis. 2013;72.

136. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis. 2013;72(1):43-50.

137. Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. Ann Rheum Dis. 2014;73(5):803-9.

138. Kameda H, Wada K, Takahashi Y, Hagino O, van Hoogstraten H, Graham N, et al. Sarilumab monotherapy or in combination with non-methotrexate disease-modifying antirheumatic drugs in active rheumatoid arthritis: a Japan phase 3 trial (HARUKA). Mod Rheumatol. 2020;30(2):239-48.

139. Genovese MC, Fleischmann R, Kivitz A, Lee EB, van Hoogstraten H, Kimura T, et al. Efficacy and safety of sarilumab in combination with csDMARDs or as monotherapy in subpopulations of patients with moderately to severely active rheumatoid arthritis in three phase III randomized, controlled studies. Arthritis Res Ther. 2020;22(1):139.

140. Burmester GR, Bykerk VP, Buch MH, Tanaka Y, Kameda H, Praestgaard A, et al. Sarilumab monotherapy vs sarilumab and methotrexate combination therapy in patients with rheumatoid arthritis. Rheumatology (Oxford). 2022;61(6):2596-602.

141. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017;390(10093):457-68.

142. Strand V, Mysler E, Moots RJ, Wallenstein GV, Demasi R, Gruben D, et al. Patient-reported outcomes for tofacitinib with and without methotrexate, or adalimumab with methotrexate, in rheumatoid arthritis: a phase IIIB/IV trial. RMD open. 2019;5(2): e001040.

143. Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyoizumi S, Zwillich S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. Mod Rheumatol. 2015;25(4):514-21.

144. Strand V, Kremer J, Wallenstein G, Kanik KS, Connell C, Gruben D, et al. Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs. Arthritis Res Ther. 2015;17:307.

145. Smolen J, Emery P, Rigby W, Tanaka Y, Ignacio Vargas J, Damjanov N, et al. Upadacitinib as monotherapy in patients with rheumatoid arthritis: results at 48 weeks. Arthritis Rheumatol.2019;71:865-7.

146. Strand V, Buch M, Tundia N, Camp HS, Suboticki J, Goldschmidt D, et al. Upadacitinib monotherapy improves patient-reported outcomes in patients with rheumatoid arthritis and inadequate response to methotrexate. Arthritis Rheumtol. 2018;70:2833-4.

147. Scott DL, Ibrahim F, Farewell V, O'Keeffe AG, Walker D, Kelly C, et al. Tumour necrosis factor inhibitors versus combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT non-inferiority randomised controlled trial. BMJ. 2015; 350:h1046.

148. van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Cöster L, Waltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet. 2009;374(9688):459-66.

149. van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012;379(9827):1712-20.

150. Machado DA, Guzman RM, Xavier RM, Simon JA, Mele L, Pedersen R, et al. Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. J Clin Rheumatol. 2014;20(1):25-33.

151. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369(4):307-18.

152. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum. 2012;64(9):2824-35.

153. Wijesinghe H, Galappatthy P, de Silva R, Seneviratne SL, Saravanamuttu U, Udagama P, et al. Leflunomide is equally efficacious and safe compared to low dose rituximab in refractory rheumatoid arthritis given in combination with methotrexate: results from a randomized double blind controlled clinical trial. BMC Musculoskelet Dis. 2017;18(1):310.

154. Ostergaard M, van Vollenhoven RF, Rudin A, Hetland ML, Heiberg MS, Nordström DC, et al. Certolizumab pegol, abatacept, tocilizumab or active conventional treatment in early rheumatoid arthritis: 48-week clinical and radiographic results of the investigator-initiated randomised controlled NORD-STAR trial.Ann Rheum Dis. 2023;82(10):1286-95.

155. Dumitru RB, Horton S, Hodgson R, Wakefield RJ, Hensor EMA, Emery P, et al. A prospective, single-centre, randomised study evaluating the clinical, imaging and immunological depth of remission achieved by very early versus delayed Etanercept in patients with Rheumatoid Arthritis (VEDERA). BMC Musculoskelet Disord. 2016:17:61.

156. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;374(9685):210-21.

157. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516-23.

158. Takeuchi T, Tanaka Y, Amano K, Hoshi D, Nawata M, Nagasawa H, et al. Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients--REACTION 52-week study. Rheumatology (Oxford). 2011;50(10):1908-15.

159. Bykerk VP, Ostör AJ, Alvaro-Gracia J, Pavelka K, Ivorra JA, Graninger W, et al. Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. Ann Rheum Dis. 2012;71(12):1950-4.

160. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs. A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006;54(9):2807-16.

161. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. New England J Med. 2005;353(11):1114-23.

162. Westhovens R, Cole JC, Li T, Martin M, Maclean R, Lin P, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology (Oxford). 2006;45(10):1238-46.

163. Schiff M, Pritchard C, Huffstutter JE, Rodriguez-Valverde V, Durez P, Zhou X, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Ann Rheum Dis. 2009;68(11):1708-14.

164. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793-806.

165. Keystone E, Burmester GR, Furie R, Loveless JE, Emery P, Kremer J, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008;59(6):785-93.

166. Fleischmann R, van Adelsberg J, Lin Y, Castelar-Pinheiro GD, Brzezicki J, Hrycaj P, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Arthritis Rheumatol. 2017;69(2):277-90.

167. Strand V, Reaney M, Chen CI, Proudfoot CWJ, Guillonneau S, Bauer D, et al. Sarilumab improves patient-reported outcomes in rheumatoid arthritis patients with inadequate response/intolerance to tumour necrosis factor inhibitors. RMD open. 2017;3(1):e000416.

168. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet. 2013;381(9865):451-60.

169. Gottenberg JE, Brocq O, Perdriger A, Lassoued S, Berthelot JM, Wendling D, et al. NonTNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug: a randomized clinical trial. JAMA.2016;316(11):1172-80.

170. Strand V, Burmester GR, Zerbini CA, Mebus CA, Zwillich SH, Gruben D, et al. Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. Arthritis Care Res. 2015;67(4):475-83.

171. Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet. 2018;391(10139):2513-24.

172. Dörner T, Schulze-Koops H, Burmester GR, Iking-Konert C, Schmalzing M, Engel A, et al. Early and late responses in patients with rheumatoid arthritis who were conventional synthetic disease-modifying anti-rheumatic drug inadequate responders and were treated with tocilizumab or switched to rituximab: an open-label phase 3 trial (MIRAI). Clin Exp Rheumatol. 2019;37(6):937-45.

173. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med. 2016;374(13):1243-52.

174. Emery P, van Hoogstraten H, Thangavelu K, Mangan E, St John G, Verschueren P. Subcutaneous sarilumab in patients with rheumatoid arthritis who previously received subcutaneous sarilumab or intravenous tocilizumab. An open-label extension of a randomized clinical trial. ACR Open Rheumatol.2020;2(11):672-80.

175. Verschueren P, Emery P, van Hoogstraten H, et al. THU0215 efficacy of sarilumab in patients with rheumatoid arthritis with and without previous response to tocilizumab. Ann Rheum Dis 2018;77:A327.

176. Fleischmann RM, Genovese MC, Enejosa JV, Mysler E, Bessette L, Peterfy C, Durez P, et al. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. Ann Rheum Dis. 2019;78(11):1454-62.

177. Smolen JS, Burmester GR, Combe B, Curtis JR, Hall S, Haraoui B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. 2016;388(10061):2763-74.

178. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD; BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003;48(8):2122-7.

179. Mariette X, Förger F, Abraham B, Flynn AD, Moltó A, Flipo RM, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis. 2018;77(2):228-33.

180. Craddle Clowse ME, Förger F, Hwang C, Thorp J, Dolhain RJ, van Tubergen A, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis. 2017;76(11):1890-6.

181. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013;65(1):28-38.

182. Schiff M, Weinblatt ME, Valente R, van der Heijde D, Citera G, Elegbe A, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis. 2014;73(1):86-94.

183. Schiff M, Weinblatt ME, Valente R, Citera G, Maldonado M, Massarotti E, et al. Reductions in disease activity in the AMPLE trial: clinical response by baseline disease duration. RMD Open. 2016;2(1):e000210.

184. Rigby W, Buckner JH, Louis Bridges S, Nys M, Gao S, Polinsky M, et al. HLA-DRB1 risk alleles for RA are associated with differential clinical responsiveness to abatacept and adalimumab: data from a head-to-head, randomized, single-blind study in autoantibody-positive early RA. Arthritis Res Ther. 2021;23(1):245.

185. Weinblatt M, Emery P, Bykerk V, Cope A, Burmester G, Tanaka Y, et al. Subcutaneous abatacept vs adalimumab head-to-head comparison in adults with early, dual seropositive rheumatoid arthritis, positive for the shared epitope HLA class II risk alleles, and an inadequate response to methotrexate. Results from a phase 3 trial. Arthritis Rheumatol. 2024; 76 (Suppl 9):#2671.

186. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381(9877):1541-50.

187. Strand V, Michalska M, Birchwood C, Pei J, Tuckwell K, Finch R, et al. Impact of tocilizumab monotherapy on patient-reported outcomes in patients with rheumatoid arthritis from two randomised controlled trials. RMD open. 2017;3(2):e000496.

188. Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NM, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis 2017;76(5):840-7.

189. Giles JT, Sattar N, Gabriel S, Ridker PM, Gay S, Warne C, et al. Cardiovascular safety of tocilizumab versus etanercept in rheumatoid arthritis: a randomized controlled trial. Arthritis Rheumatol. 2020;72(1):31-40.

190. van Vollenhoven R, Cohen S, Mendelsohn A, Bananis E, Fan H, Takiya L, et al. Efficacy of adalimumab and tofacitinib in rheumatoid arthritis: Post-Hoc analyses freom a phase 3 study. POST HOC ORAL STANDARD. Ann Rheum Dis. 2016;75(Suppl 2):1042.

191. Strand V, van Vollenhoven RF, Lee EB, Fleischmann R, Zwillich SH, Gruben D, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. Rheumatology. 2016;55(6):1031-41.

192. Strand V, Mysler E, Moots RJ, Wallenstein G, DeMasi R, Gruben D, et al. Tofacitinib with and without methotrexate versus adalimumab with methotrexate for the treatment of rheumatoid arthritis: patient-reported outcomes from a phase 3b/4 randomised trial. Ann Rheum Dis. 2018;77:990-1.

193. Fleischmann R, Enejosa JJ, Song I-H, Mysler E, Bessette L, Peterfy C, et al. Safety and effectiveness of upadacitinib or adalimumab in patients with rheumatoid arthritis: results at 48 weeks. SELECT COMPARE. Arthritis Rheumatol. 2019;71(11):1788-800.

194. Rubbert-Roth A, Enejosa J, Pangan AL, Haraoui B, Rischmueller M, Khan N, et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. N Engl J Med. 2020;383(16):1511-21.

195. Bergman M, Enejosa J, Martin N, Suboticki J, Goldschmidt D, Song Y, et al. Patient-reported outcomes of upadacitinib versus abatacept in patients with rheumatoid arthritis and an inadequate response to biologic disease-modifying antirheumatic drugs: 12-eeek results of a phase 3 study SELECT CHOICE. Arthritis Rheumatol. 2020;72(Suppl 10):3488-9.

196. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. New Engl J Med. 2017;376(7):652-62.

197. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med. 2022;386(4):316-326.

198. Herrinton LJ, Harrold LR, Liu L, Raebel MA, Taharka A, Winthrop KL, et al. Association between anti-TNF-α therapy and interstitial lung disease. Pharmacoepidemiol Drug Saf. 2013;22(4):394-402.

199. Detorakis EE, Magkanas E, Lasithiotaki I, Sidiropoulos P, Boumpas DT, Gourtsoyiannis N, et al. Evolution of imaging findings, laboratory and functional parameters in rheumatoid arthritis patients after one year of treatment with anti-TNF-α agents. Clin Exp Rheumatol. 2017;35(1):43-52.

200. Nakashita T, Ando K, Kaneko N, Takahashi K, Motojima S. Potential risk of TNF inhibitors on the progression of interstitial lung disease in patients with rheumatoid arthritis. BMJ Open. 2014;4(8):e005615.

201. Koo BS, Hong S, Kim YJ, Kim YG, Lee CK, Yoo B. Mortality in patients with rheumatoid arthritis-associated interstitial lung disease treated with an anti-tumor necrosis factor agent. J Korean Med Sci. 2015;30(1):104-9.

202. Huang Y, Lin W, Chen Z, Wang Y, Huang Y, Tu S. Effect of tumor necrosis factor inhibitors on interstitial lung disease in rheumatoid arthritis: angel or demon? Drug Des Devel Ther. 2019;13:2111-25.

203. Akiyama M, Kaneko Y, Yamaoka K, Kondo H, Takeuchi T. Association of disease activity with acute exacerbation of interstitial lung disease during tocilizumab treatment in patients with rheumatoid arthritis: a retrospective, case-control study. Rheumatol Int. 2016;36(6):881-9.

204. Manfredi A, Cassone G, Furini F, Gremese E, Venerito V, Atzeni F, et al. Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicentre retrospective study. Intern Med J. 2020;50(9):1085-90.

205. Ibfelt EH, Jacobsen RK, Kopp TI, Cordtz RL, Jakobsen AS, Seersholm N, et al. Methotrexate and risk of interstitial lung disease and respiratory failure in rheumatoid arthritis: a nationwide population-based study. Rheumatology (Oxford). 2021;60(1):346-52.

206. Kiely P, Busby AD, Nikiphorou E, Sullivan K, Walsh DA, Creamer P, et al. Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. BMJ Open. 2019;9(5):e028466.

207. Kim K, Woo A, Park Y, Yong SH, Lee SH, Lee SH, et al. Protective effect of methotrexate on lung function and mortality in rheumatoid arthritis-related interstitial lung disease: a retrospective cohort study. Ther Adv Respir Dis. 2022;16:17534666221135314.

208. Sawada T, Inokuma S, Sato T, Otsuka T, Saeki Y, Takeuchi T, et al. Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. Rheumatology (Oxford). 2009;48(9):1069-72.

209. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Leflunomide use and risk of lung disease in rheumatoid arthritis. A systematic literature review and metaanalysis of randomized controlled trials. J Rheumatol. 2016 May;43(5):855-60.

210. Md Yusof MY, Kabia A, Darby M, Lettieri G, Beirne P, Vital EM, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology (Oxford). 2017;56(8):1348-57.

211. Duarte AC, Porter JC, Leandro MJ. The lung in a cohort of rheumatoid arthritis patients-an overview of different types of involvement and treatment. Rheumatology (Oxford). 2019;58(11):2031-8.

212. Fui A, Bergantini L, Selvi E, Mazzei MA, Bennett D, Pieroni MG, et al. Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. Intern Med J. 2020;50(3):330-6.

213. Narváez J, Robles-Pérez A, Molina-Molina M, Vicens-Zygmunt V, Luburich P, Yañez MA, et al. Real-world clinical effectiveness of rituximab rescue therapy in patients with progressive rheumatoid arthritis-related interstitial lung disease. Semin Arthritis Rheum. 2020;50(5):902-10.

214. Kelly CA, Nisar M, Arthanari S, Carty S, Woodhead FA, Price-Forbes A, et al. Rheumatoid arthritis related interstitial lung disease - improving outcomes over 25 years: a large multicentre UK study. Rheumatology (Oxford). 2021;60(4):1882-90.

215. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. Respir Investig. 2016;54(5):376-9.

216. Fernández-Díaz C, Loricera J, Castañeda S, López-Mejías R, Ojeda-García C, Olivé A, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients. Semin Arthritis Rheum. 2018;48(1):22-7.

217. Mochizuki T, Ikari K, Yano K, Sato M, Okazaki K. Long-term deterioration of interstitial lung disease in patients with rheumatoid arthritis treated with abatacept. Mod Rheumatol. 2019;29(3):413-7.

218. Cassone G, Manfredi A, Atzeni F, Venerito V, Vacchi C, Picerno V, et al. Safety of abatacept in Italian patients with rheumatoid arthritis and interstitial lung disease. A multicenter retrospective study. J Clin Med. 2020;9(1):277.

219. Fernández-Díaz C, Castañeda S, Melero-González RB, Ortiz-Sanjuán F, Juan-Mas A, Carrasco-Cubero C, et al. Abatacept in interstitial lung disease associated with rheumatoid arthritis: national multicenter study of 263 patients. Rheumatology (Oxford). 2020;59(12):3906-16.

220. Tardella M, Di Carlo M, Carotti M, Giovagnoni A, Salaffi F. Abatacept in rheumatoid arthritis-associated interstitial lung disease: short-term outcomes and predictors of progression. Clin Rheumatol. 2021;40(12):4861-7.

221. Fernández-Díaz C, Atienza-Mateo B, Castañeda S, Melero-Gonzalez RB, Ortiz-SanJuan F, Loricera J, et al. Abatacept in monotherapy vs combined in interstitial lung disease of rheumatoid arthritis-multicentre study of 263 Caucasian patients. Rheumatology (Oxford). 2021;61(1):299-308.

222. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. Inflammopharmacology. 2022;30(3):705-12.

223. Matteson E, Kelly C, Distler J, Hoffmann-Vold AM, Seibold J, Mittoo S, et al. Effect of nintedanib on progression of interstitial lung disease (ILD) in patients with autoimmune disease-related ILDS: further data from the inbuild trial. Ann Rheum Dis. 2020;79(Suppl 1):76.

224. Dellaripa P, Hoffmann-Vold A, Kelly C, Mittoo S, James A, et al. Effects of nintedanib in patients with progressive fibrosing autoimmune disease-related interstitial lung diseases (ILDs) in the INBUILD trial: subgroups by HRCT pattern [abstract]. Arthritis Rheumatol. 2020;72(Suppl 10).

225. Smith V, Assassi S, Allanore Y, Loaiza L, Tschoepe I, Kanakapura M, et al. Safety and tolerability of nintedanib in patients with autoimmune disease-related interstitial lung diseases: pooled data from the senscis and inbuild trials. Arthritis Rheumatol. 2021;73(Suppl 9):374-5.

226. Dellaripa P, Doyle T, Danoff S, Goldberg H, Kolb M, Chambers D, et al. The performance of RA disease activity and patient-reported outcomes in rheumatoid arthritis-associated interstitial lung disease in a prospective trial using pirfenidone in RA ILD (trail1). Arthritis Rheumatol. 2021;73(Suppl 9):1547-9.

227. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363(3):221-32

228. Puéchal X, Gottenberg JE, Berthelot JM, Gossec L, Meyer O, Morel J, et al. Rituximab therapy for systemic vasculitis associated with rheumatoid arthritis. Results from the AutoImmunity and Rituximab Registry. Arthritis Care Res (Hoboken). 2012;64(3):331-9.

229. Coffey CM, Richter MD, Crowson CS, Koster MJ, Warrington KJ, Ytterberg SR, et al. Rituximab therapy for systemic rheumatoid vasculitis: indications, outcomes, and adverse events. J Rheumatol. 2020;47(4):518-23.

230. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Bahlas S, Hegazi M, et al. Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission. Clinical Rheumatol. 2016;35(12):2915-23.

231. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet. 2013;381(9870):918-29.

232. Kaine J, Gladstein G, Strusberg I, Robles M, Louw I, Gujrathi S, et al. Evaluation of abatacept administered subcutaneously in adults with active rheumatoid arthritis: impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (phase Iiib ALLOW study). Ann Rheum Dis. 2012;71(1):38-44.

233. Emery P, Tanaka Y, Bykerk V, Huizinga T, Citera G, Bingham C, et al. Maintenance of SDAI remission and patient-reported outcomes (PROS) following dose de-escalation of abatacept in MTX-NAÏVE, anti-citrullinated protein antibody (ACPA)+ patients with EARLY RA: results from AVERT-2, a randomised phase IIIB study. Ann Rheum Dis. 2020;79:985.

234. Smolen JS, Emery P, Fleischmann R, van Vollenhoven RF, Pavelka K, Durez P, et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. Lancet. 2014;383(9914):321-32.

235. van Vollenhoven RF, Østergaard M, Leirisalo-Repo M, Uhlig T, Jansson M, Larsson E, et al. Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. Ann Rheum Dis. 2016;75(1):52-8.

236. Chatzidionysiou K, Turesson C, Teleman A, Knight A, Lindqvist E, Larsson P, et al. A multicentre, randomised, controlled, open-label pilot study on the feasibility of discontinuation of adalimumab in established patients with rheumatoid arthritis in stable clinical remission. RMD Open. 2016;2(1):e000133.

237. Wakabayashi H, Nagao N, Inada H, Nishioka Y, Hasegawa M, Nishioka K, et al. Long-term maintenance of golimumab effectiveness for injection spacing in rheumatoid arthritis patients with low disease activity who previously received other TNF inhibitors. Minimum 2-year data from an observational study. Drugs R D. 2021;21(3):351-7.

238. Yoshida S, Kotani T, Kimura Y, Matsumura Y, Yoshikawa A, Tokai N, et al. Efficacy of abatacept tapering therapy for sustained remission in patients with rheumatoid arthritis: Prospective single-center study. Int J Rheum Dis. 2019;22(1):81-9.

239. Bouman CAM, Tweehuysen L, Haverkort D, van den Ende CH, van der Maas A, den Broeder AA. Abatacept and tocilizumab tapering in rheumatoid arthritis patients: results of SONATA-a retrospective, exploratory cohort study. Rheumatol Adv Pract. 2018;2(1):rky008.

240. Ibrahim F, Lorente-Canovas B, Dore CJ, Bosworth A, Ma MH, Galloway JB, et al. Optimizing treatment with tumour necrosis factor inhibitors in rheumatoid arthritis-a proof of principle and exploratory trial: is dose tapering practical in good responders? Rheumatology (Oxford). 2017;56(11):2004-14.

241. Bejerano C, Oreiro N, Fernández-López C, Pinto-Tasende JA, Atanes A, De Aspe B, et al. Clinical evaluation usefulness of standardized protocol strategies of dose reduction in patients with rheumatoid arthritis in clinical remission treated with biologic therapies. The optibio study. Arthritis Rheumatol. 2016;68:853-5.

242. Fautrel B, Pham T, Alfaiate T, Gandjbakhch F, Foltz V, Morel J, et al. Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: spacing of TNF-blocker injections in Rheumatoid ArthritiS Study). Ann Rheum Dis. 2016;75(1):59-67.

243. van Herwaarden N, van der Maas A, Minten MJ, van den Hoogen FH, Kievit W, van Vollenhoven RF, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. BMJ. 2015;350:h1389.

244. Sanmarti R, Veale DJ, Martin-Mola E, Escudero-Contreras A, González C, Ercole L, et al. Reducing or maintaining the dose of subcutaneous tocilizumab in patients with rheumatoid arthritis. Arthritis Rheumatol. 2019;71(10):1616-25.

245. Pablos JL, Navarro F, Blanco FJ, Román-Ivorra JA, Alonso A, Martín Mola E, et al. Efficacy of tocilizumab monotherapy after response to combined tocilizumab and methotrexate in patients with rheumatoid arthritis: the randomised JUST-ACT study. Clin Exp Rheumatol. 2019;37(3):437-44.

246. Cohen SB, Pope J, Haraoui B, Mysler E, Diehl A, Lukic T, et al. Efficacy and safety of tofacitinib modified-release 11 mg once daily plus methotrexate in adult patients with rheumatoid arthritis: 24-week open-label phase results from a phase 3b/4 methotrexate withdrawal non-inferiority study (ORAL Shift). RMD Open. 2021;7(2) :e001673.

247. van Mulligen E, Weel AE, Hazes JM, van der Helm-van Mil A, de Jong PHP. Tapering towards DMARD-free remission in established rheumatoid arthritis: 2-year results of the TARA trial. Ann Rheum Dis. 2020;79(9):1174-81.