EULAR 2004: magna cita de la Reumatología

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La artritis reumatoide (AR) es una enfermedad autoinmune que afecta al 1% de la población mundial. Provoca dolor, inflamación y rigidez en las articulaciones de las manos, los pies, las muñecas y las rodillas, y finalmente ocasiona la destrucción articular. Los pacientes que la padecen están expuestos a una discapacidad funcional progresiva, que implica un aumento considerable de la morbilidad y un gasto sanitario tanto directo como indirecto.

El principal objetivo de la terapia para esta enfermedad es disminuir los síntomas, lo que significa disminuir el dolor, la inflamación y la incapacidad funcional en los pacientes. Otro objetivo vital de la terapia es prevenir la progresión de la enfermedad, lo que implica inhibir la progresión de los daños estructurales de la articulación y mejorar la calidad de vida.

Los medicamentos históricamente empleados en el tratamiento de la AR incluyen los compuestos antiinflamatorios no esteroideos (AINE, siglas en inglés), que permiten aliviar los síntomas y las llamadas drogas antirreumáticas modificadoras de la enfermedad (DMARD, siglas en inglés). Las DMARD han resultado exitosas en la mejoría de las características clínicas de la enfermedad y efectivas en las etapas tempranas. Sin embargo, con el tiempo, la eficacia de estas drogas resulta limitada y aparecen efectos de toxicidad. Además, este tipo de droga es incapaz de detener el proceso de destrucción de la articulación.

Recientemente surgió un nuevo tipo de terapia: la terapia biológica, la cual se refiere a estrategias de tratamiento con el empleo de compuestos generados por las células vivas, en contraste con los fármacos convencionales que son generados por síntesis química. Esta terapia es el resultado de los avances alcanzados en la comprensión de los mecanismos moleculares que gobiernan los eventos patológicos en el sinovio inflamado y de la aplicación de la biotecnología en el desarrollo de terapias dirigidas específicamente contra células y moléculas que participan en el inicio y mantenimiento de la respuesta inflamatoria en la AR.

El Congreso Anual Europeo de Reumatología es el evento internacional de mayor impacto y relevancia científica en el tema de las enfermedades reumáticas hoy, organizado por la Liga Europea contra el Reumatismo (EULAR, siglas en inglés). El propósito del evento es concertar un fórum de alto nivel, en los aspectos clínicos y básicos de la rama de las enfermedades reumáticas, para el intercambio entre científicos, médicos y pacientes. Este año se celebró la quinta edición, del 9 al 12 de junio en el Centro Internacional de Congresos de Berlín, Alemania.

En esta cita se reunieron más de 4 000 delegados de Europa, Estados Unidos, América Latina, Asia y África. Las 110 sesiones científicas del congreso estuvieron conformadas por 170 conferencias, 180 presentaciones orales y alrededor de 2 000 presentaciones en carteles. Adicionalmente se organizaron 22 simposios satélites en los que importantes firmas comerciales como ABBOTT Laboratories (Estados Unidos), AMGEN EUROPE (Holanda), ANAMAR MEDICAL AB (Suecia), ASTRAZENECA (Suecia), AVENTIS (Francia), BOEHRINGER INGELHEIM (Alemania) y ELI LILLY & Company (Estados Unidos) presentaron los principales avances alcanzados en el desarrollo de medicamentos y la creación de accesorios y equipos destinados al tratamiento y mejoramiento de la calidad de vida de las personas que padecen enfermedades reumáticas.

El programa científico incluyó entre sus tópicos más relevantes los aspectos moleculares y celulares de las enfermedades reumáticas, los aspectos clínicos de los desórdenes musculosqueléticos y los avances en la investigación en los servicios de salud, educación y epidemiología. Aunque el espectro de enfermedades reumáticas abordado fue amplio: osteoartritis, vasculitis, osteoporosis, espondiloartritis, artritis psoriásica, síndrome de Sjögren, esclerosis sistémica, aterosclerosis, fibromialgia y lupus eritematoso sistémico. La artritis reumatoide fue tratada con especial atención desde el punto de vista clínico y su tratamiento.

*T*erapias anticitocinas en artritis reumatoide

Aunque la patogénesis de la AR no está completamente clara, durante la última década los investigadores han logrado entender mejor los mecanismos celulares y moleculares implicados en la enfermedad. En el origen y desarrollo de esta enfermedad se destacan dos citocinas proinflamatorias: el factor de necrosis tumoral alfa (TNF-α) y la interleucina-1 (IL-1). Por esta razón, ambas constituyen los principales blancos de las terapias biológicas existentes en la actualidad para el tratamiento de la AR.

Antagonistas del TNF-α

El TNF-α desempeña una función primaria en la cascada de citocinas en la AR, pues controla la producción de IL-1 y estimula otras citocinas proinflamatorias como la IL-6 y la IL-8 [1, 2]. Además, induce a los sinoviocitos a liberar sustancias involucradas en la degradación del

1. Brennan FM. Inhibitory effect of TNF-a antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. Lancet 1989;2:244-7.

2. Butler DM. Modulation of proinflammatory cytokines release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF-a antibody with the interleukin-1 receptor antagonist. Eur Cytokine Netw 1995;6: 225-30.

tejido, permite a las células inmunocompetentes infiltrar el espacio articular y adherirse al sinovio, lo que ocasiona el crecimiento anormal del cartílago y la erosión del hueso. En modelos experimentales de artritis se ha demostrado la importancia patogénica del TNF-α y la eficacia terapéutica de su inhibición [3, 4].

Durante las sesiones de EULAR 2004 se dedicó especial atención al uso de los antagonistas del TNF-α con licencia, disponibles actualmente en el mercado: etanercept (Enbrel, nombre comercial), infliximab (Remicade, nombre comercial) y adalimumab (Humira, nombre comercial). El etanercept es un receptor recombinante humano del TNF, mientras que el infliximab es un anticuerpo monoclonal parcialmente humanizados; ambos dirigidos a reducir la acción del TNF-α circulante en sangre. Ambos producen su efecto al bloquear el TNF-α de la circulación sanguínea y, consecuentemente, interrumpir el proceso inflamatorio. El adalimumab es el primer anticuerpo monoclonal dirigido a realizar una acción específica, desarrollado completamente a partir de células humanas y aprobado por la Administración de Drogas y Alimentos de los Estados Unidos (FDA, siglas en inglés), para la reducción de los síntomas y la inhibición del progreso de la AR en adultos.

Los ensayos clínicos iniciales con estas drogas se han conducido con pacientes que presentan severidad en la enfermedad y en condiciones óptimas controladas, lo que no es reflejo de la práctica clínica diaria. De varios de estos estudios ha quedado claro que la oportunidad de frenar su desarrollo existe entre el inicio de los síntomas y el inicio del daño articular, y que una intervención temprana determina el resultado final. Además, se ha demostrado que los antagonistas del TNF-α son una vía para cambiar el curso de la enfermedad y ofrecen la posibilidad, incluso, de una remisión total. A la luz de este conocimiento se han trazado nuevas estrategias en el tratamiento de la AR.

Por primera vez en el marco de estos eventos se presentó un estudio que evalúa simultáneamente cuatro estrategias de tratamiento agresivo de la AR temprana. Estas incluyen la monoterapia secuencial, la terapia escalonada, la terapia inicial combinada y la terapia inicial biológica con el empleo de medicamentos inmunosupresores y antirreumáticos como el metotrexato, la leflunomida, la ciclosporina A y la sulfazalacina en combinación con el infliximab (Figura 1). El ensayo clínico BeST es un estudio aleatorio y controlado, que evalúa la habilidad funcional del paciente y el daño articular. Los resultados del primer año del ensayo en curso demuestran que la terapia basada en la combinación inicial y la terapia biológica inicial ofrecen un mejor índice de la calidad de la salud, así como una progresión más lenta de los daños articulares, sin efectos adversos graves y una mayor satisfacción del paciente, que cuando se emplean la monoterapia o la terapia escalonada.

Otro ensayo clínico con el empleo de un antagonista del TNF-α presentado durante EULAR 2004, es el estudio TEMPO. En este se realiza una comparación entre el uso independiente del

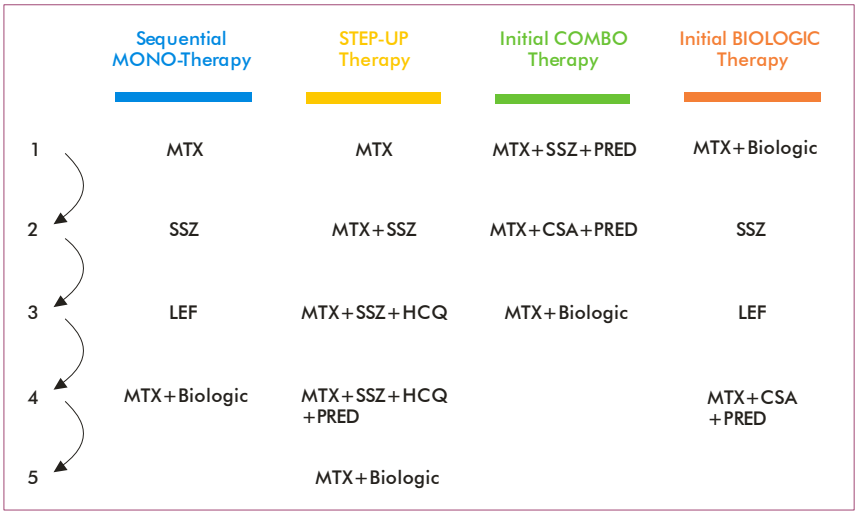

Figura 1. Ensayo clínico BeST. Estrategias agresivas para el tratamiento de la AR temprana. MTX-metotrexato, SSZ-sulfazalacina, LEF-leflunomida, HCQ-hidroxicloroquina, PRED-prednisona, CSA-ciclosporina A, Biologic-Infliximab. Tomado de: Smolen J.S. *et al*. (2003) Clin Exp Rheumatol 21 (Suppl 31); 5209-12. Resumen aceptado en EULAR 2004.

etanercept y del metotrexato y la combinación de ambos. Se presentaron los datos de la evaluación de eficacia y seguridad después de dos años de tratamiento a pacientes que padecen AR activa, a los cuales les ha fallado una terapia previa con DMARD, diferente del metotrexato. Adicionalmente se evaluó el estado funcional de los pacientes. TEMPO es un estudio a doble ciegas, aleatorio, y que incluye más de 600 pacientes, en el cual se valoran los criterios de respuesta ACR20, ACR50 y ACR70 establecidos por el Colegio Americano de Reumatología: (ACR, siglas de *American College of Rheumatology*) (Figura 2)

3. Keffer K, Probert L, Cazlaris H. Transgenic mice expressing human tumor necrosis factor: a predictive genetic model of arthritis. EMBO J 10 (1991):4025-31.

4. Feldman M, Brennam FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol 1996;14:397-440.

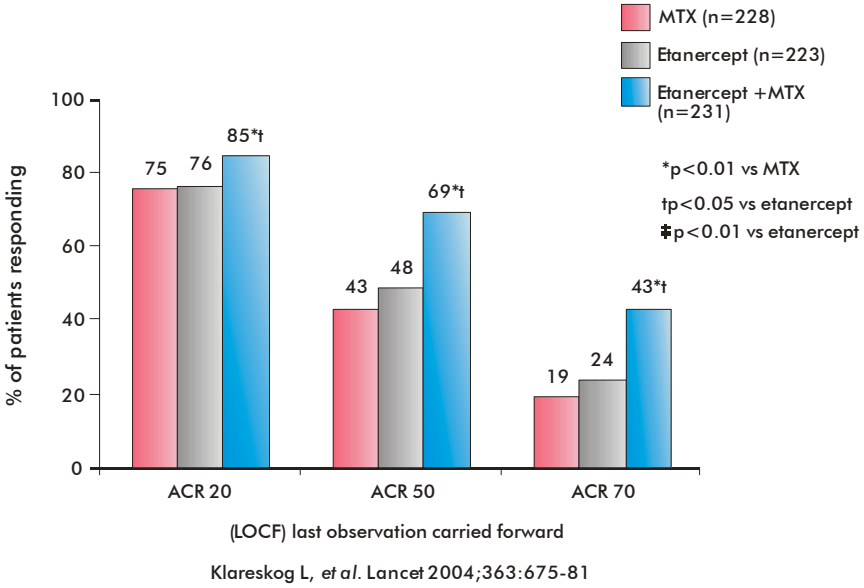

Figura 2. Ensayo clínico TEMPO. Evaluación de la eficacia del tratamiento independiente con metotrexato, Etanercept y la combinación de ambos mediante los criterios de respuesta ACR20, ACR50 y ACR70. MTX-metotrexato. ACR-criterio de respuesta del Colegio Americano de Reumatología. Tomado de: Klareskog, L. et al. (2004) Lancet 363: 675-81. Resumen aceptado en EULAR 2004.

índice de remisión (DAS, siglas de *Disease Activity Score*, índice de la actividad de la enfermedad), índice de calidad de salud (HAQ, siglas de *Health Assessment Questionnaire*, cuestionarios de percepción de salud) y los niveles de proteína C reactiva, cuya presencia se correlaciona con la progresión radiográfica del daño articular en la AR. En este ensayo se demostró que la respuesta clínica óptima se obtiene cuando se combinan el etanercept y el metotrexato: se logra reducir la actividad de la enfermedad sin aparente incremento de la toxicidad, se mejora la capacidad funcional de los pacientes y se retarda la progresión del daño articular. Estos resultados ubican la estrategia empleada más cerca del objetivo final de la terapia para la AR: la remisión de la enfermedad.

Otra presentación de relevancia en EULAR 2004 fue el ensayo clínico ReAct que emplea adalimumab, el más reciente antagonista del TNF-α aprobado para el uso en humanos. ReAct (de Research in Active RA, investigación en AR activa) es un ensayo abierto y con características de vida real. Es de mayor alcance que se está llevando a cabo en Europa con el empleo de este antagonista del TNF-α. En él participan 6 000 pacientes de más de 11 países europeos, atendidos en más de 400 centros de salud. Se presentaron los datos del análisis inicial de los primeros 2 008 pacientes. En este grupo, la edad promedio fue de 53 años, y el 80% de los pacientes fueron mujeres, con un promedio de 11 años de duración de la enfermedad. Las personas evaluadas tenían una AR clasificada de moderada a severa y una respuesta inadecuada a la terapia antirreumática estándar. Estos pacientes fueron tratados con 40 mg de adalimumab, suministrado de forma subcutánea en semanas alternas. La evaluación de la eficacia y seguridad del tratamiento se realizó en las semanas 2, 6 y 12 (Figuras 3 y 4). Ellos experimentaron, además, una reducción sustancial de los signos y síntomas de la enfermedad. La mejoría se evidenció según los criterios ACR, DAS y la medición del dolor. De los 2 008 pacientes evaluados inicialmente,

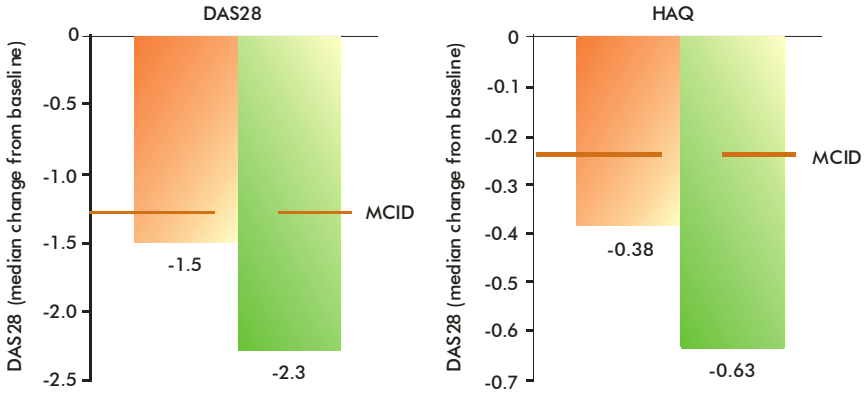

Figura 4. Ensayo clínico ReAct. Evaluación del índice de remisión y el índice de calidad de salud mediante los parámetros DAS (Disease Activity Score-índice de la actividad de la enfermedad) y HAQ (Health Assessment Questionnaire-cuestionario de percepción de salud). Tomado de: Goldsmith, C. et al. (1993) J Rheum 20: 561-5. Resumen aceptado en EULAR 2004.

164 habían sido tratados anteriormente con una o más DMARD y 630 estaban siendo tratados al menos con una, fundamentalmente el metotrexato. El empleo del adalimumab demostró alta eficacia en pacientes que habían tenido experiencias anteriores con otros medicamentos de tipo biológico (Figura 5). En este ensayo quedó demostrado que una simple dosis de 40 mg de adalimumab administrada a los pacientes con AR ofreció una rápida mejoría (posterior a las dos primeras semanas del inicio del tratamiento) en los principales parámetros de eficacia, la cual persistió durante el tratamiento continuado.

En EULAR 2004, a partir de los resultados de los ensayos clínicos y otros trabajos que emplean los antagonistas del TNF-α, quedó confirmado que los tratamientos aplicados hasta el momento provocan reacciones adversas; entre ellas, infecciones oportunistas, linfomas, falla cardíaca congestiva, desarrollo de otros procesos autoinmunes, demielinación y reacciones locales en el sitio de la administración. A pesar de ello, las consideraciones finales sobre el empleo de los antagonistas del TNF-α en todos los casos

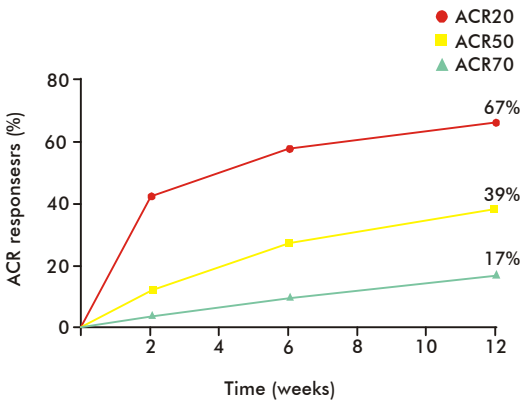

Figura 3. Ensayo clínico ReAct. Evaluación de la eficacia del tratamiento con Adalimumab. ACR-criterio de respuesta del Colegio Americano de Reumatología. Burmester, G.R. et al. Resumen aceptado en EULAR 2004.

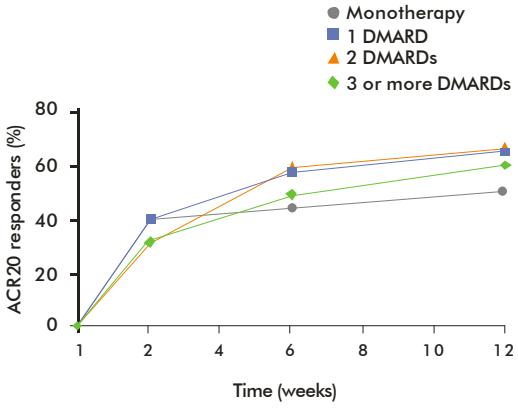

Figura 5. Ensayo clínico ReAct. Eficacia del tratamiento con Adalimumab en pacientes tratados concomitantemente con 1 o mas drogas DMARDs. ACR-criterio de respuesta del Colegio Americano de Reumatología. Mariette, X. et al. Resumen aceptado en EULAR 2004.

son positivas. Esta terapia es altamente efectiva en pacientes con un diagnóstico temprano de la enfermedad y también en aquellos con AR que no han sido tratados anteriormente con DMARD. Además, se demostró que la remisión clínica y la inhibición del daño articular son objetivos plausibles con la aplicación de los antagonistas del TNF-α. El uso óptimo de estas drogas se logra con la combinación concomitante del metotrexato y en etapas tempranas de la enfermedad.

El éxito de la terapia biológica con antagonistas del TNF-α, en particular de su eficacia combinada con el actual grado de seguridad, ha demostrado que una enfermedad tan compleja como la AR puede ser modulada por una estrategia terapéutica dirigida a un aspecto específico del proceso autoinmune, que evite la inmunosupresión total de los pacientes. Esta terapia biológica se combina actualmente con drogas antirreumáticas convencionales en un intento por lograr una eficacia clínica sinérgica sin incremento de la toxicidad.

Antagonistas de la IL-1

La IL-1, de manera similar al TNF-α, induce la síntesis de las metaloproteinasas por los condorcitos y fibroblastos, acelera la angiogénesis e incrementa la expresión de moléculas de adhesión sobre el endotelio, lo cual promueve la infiltración de células al espacio extravascular [5, 6]. Además, la IL-1 inhibe la producción de colágeno y proteoglicanos y estimula la resorpción del hueso mediante la activación de los osteoclastos [7, 8].

Los receptores de las citocinas se unen a sus ligandos con alta afinidad y especificidad. Las versiones solubles de estos receptores retienen la especificidad de unión de las formas unidas a las membranas y pueden neutralizar la actividad biológica de las citocinas de manera eficiente. En la superficie de las células se han detectado dos tipos de receptores de la IL-1. El receptor tipo I es el responsable de la traducción de las señales al núcleo. Ensayos de tratamiento con el receptor I humano recombinante de la IL-1 (rhu IL-1R1) han sido exitosos en modelos experimentales como el de la artritis inducida por adyuvantes [9]. Sin embargo, la aplicación intraarticular de rhu IL-1R1 en pacientes con AR no ha mostrado los efectos terapéuticos deseados [10].

Al igual que los receptores solubles, los antagonistas de los receptores pueden bloquear las interacciones ligando-receptor y, consecuentemente, la señalización. Para que un antagonista del receptor funcione bien, este tiene que unir todos los receptores de la superficie celular y mantenerlos continuamente ocupados, lo cual puede ser difícil de lograr en la práctica clínica. Una versión recombinante del antagonista del receptor humano de la IL-1 (rHuIL-1Ra) fue evaluada en pacientes con AR [11]. El estudio aleatorio, a doble ciegas y controlado con placebo incluyó 175 pacientes y demostró que las inyecciones subcutáneas diarias de rHuIL-1Ra tenían efecto terapéutico. La mejoría clínica se observó después de dos semanas de iniciado el tratamiento y la progresión de la enfermedad se logró retardar. Un estudio similar de mayor alcance, con el empleo del rHuIL-1Ra se informó posteriormente y confirmó la eficacia y seguridad del fármaco [12]. Actualmente, el único inhibidor de la IL-1 aprobado por la FDA para el tratamiento de la AR es el anakinra (Kineret, nombre comercial). El tratamiento con este fármaco se aplica fundamentalmente a pacientes que no responden a los antagonistas del TNF-α de manera satisfactoria y requiere la administración subcutánea diaria, por lo que hoy constituye un reto encontrar una terapia eficiente dirigida contra la IL-1 y con una frecuencia menor de administración.

El trabajo presentado por Bingham y col. durante EULAR 2004 emplea una "trampa" de IL-1 (IL-1 TRAP) que actúa como un inhibidor específico y de alta afinidad de la IL-1. Es una molécula formada por la porción Fc de la IgG1 humana y los dominios extracelulares de ambos receptores de la IL-1. El ensayo es un estudio multicéntrico, aleatorio, a doble ciegas, que incluye más de 200 pacientes y evalúa la administración subcutánea semanal de placebo o de 25, 50 y 100 mg de IL-1 TRAP en pacientes con AR catalogada de moderada a severa. El resultado del estudio demostró que la dosis más elevada de IL-1 TRAP es eficaz clínica y biológicamente según la rápida y significativa reducción de los niveles de proteína C reactiva y el índice de sedimentación de eritrocitos, así como por la mejoría en el índice de actividad de la enfermedad (DAS). La droga fue bien tolerada. La reacción adversa más común fue el enrojecimiento del sitio de la administración y no se observó incremento de las infecciones oportunistas.

Otros principios terapéuticos de origen biológico aplicados a la AR

Interferencia con la interacción B7/CD28

En la patogénesis de la AR está bien definida la contribución de las células T al proceso inflamatorio. La célula T necesita dos señales para su activación. Una de ellas es inducida mediante su receptor, después que este interactúa con el péptido inmunogénico presentado por las moléculas HLA. La otra señal es inducida mediante la molécula CD28 en la célula T, después de su interacción con la molécula B7 presente en la superficie de la célula presentadora del antígeno. A la vez que la célula T se activa, se expresan cantidades incrementadas de moléculas CTLA-4. Las señales inhibitorias para la activación de la célula T se generan cuando la molécula CTLA-4 se combina con la molécula B7 en lugar de la molécula CD28. La afinidad de CTLA-4 por B7 es alrededor de 100 veces más fuerte que la afinidad de CD28 por B7 [13]. En este sentido, una estrategia terapéutica interesante es lograr la inhibición de la activación de la célula T mediante la interferencia de la interacción B7/CD28.

5. Brennam FM, Maini RN, Feldman M. Role of pro-inflammatory cytokines in rheumatoid arthritis. Springer Semin Inmunopathol 1998;20:133-47.

6. Dinarello CA, Moldawer LL. Proinflammatory and anti-inflammatory cytokines in rheumatoid arthritis. Amgen Inc.1999:19-20.

7. Adorini L, Sinigaglia F. Pathogenesis and immunotherapy of autoimmune diseases. Immunol Today 1997;18:209-11.

8. Häuselmann HJ, Flechtenmacher J, Michal L, Thonar EJ-MA, Shinmei M, Keuttner KE. The superficical layer of human articular cartilage is more susceptible to interleukin-1-induced damage than the deeper layers. Arthritis Rheum 1996;39: 478-88.

9. Fernandez-Botran R. Soluble cytokine receptors: their role in immunoregulation. FASEB J 5 1991:2567-74.

10. Drevlow B, Capezio J, Lovis R, Jacobs C, Landay A, Pope RM. Phse I study of recombinant human interleukin-1 receptor (rhu IL-1R) administered intra-articularly in active rheumatoid arthritis. Arthritis Rheum 36 1993;Suppl 9:S39.

11. Campion GV, Lebsack ME, Lookabaugh J, Gordon G, Catalano M. The IL-1Ra Arthritis Study Group. Dose-range and dose-frequency study for recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. Arthritis Rheum 1996;39:1092-101.

12. Bresniham B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41: 2196-204.

El CTLA4Ig (abatacept) es una proteína soluble de fusión, compuesta por el dominio extracelular de CTLA4 y la porción Fc de la IgG1 humana. El empleo de esta molécula para el tratamiento de la AR se expuso durante las presentaciones orales en EULAR 2004. El abatacept fue probado en un ensayo clínico fase II en pacientes con AR activa resistentes al tratamiento con metotrexato. En el ensayo, 339 pacientes con AR activa fueron tratados con dos dosis intravenosas de CTLA4Ig (10 mg/kg en semanas alternas) o placebo. A las 24 semanas de tratamiento, el 60% de los pacientes alcanzaron un índice de respuesta ACR20 y una disminución considerable de la proteína C reactiva e IL-6 en el suero. En este estudio no se reportaron efectos considerables de toxicidad. Actualmente están en análisis otros dos ensayos clínicos en fase III, con el empleo de esta molécula, cuyo objetivo principal es evaluar la eficacia y seguridad del tratamiento con metrotexato en pacientes con AR activa refractaria y en los cuales la terapia previa con antagonistas del TNF-α no ha resultado exitosa.

Otro grupo de investigadores presentaron los resultados de la eficacia del tratamiento con abatacept en combinación con el metotrexato en la AR establecida y temprana, teniendo en cuenta los resultados alcanzados por los criterios de respuesta ACR. En el ensayo aleatorio, a doble ciegas y controlado con placebo, los pacientes recibieron dosis de abatacept de 10 mg/kg con metotrexato o placebo con metotrexato. La evaluación de los criterios de respuesta ACR20, ACR50 y ACR70 se realizó a los 15 y 30 días, y posteriormente, cada 30 días, durante 12 meses. Para la evaluación de los resultados, los pacientes fueron divididos en dos grupos según la duración de la enfermedad: menos de tres años y más de tres años de duración. El resultado fue una mejoría significativa desde el punto de vista estadístico, en los criterios de respuesta ACR cuando se aplica el abatacept combinado con el metotrexato para ambos grupos en relación con el grupo que recibió placebo, y se observó una mejoría ligeramente superior en el grupo de pacientes con una menor duración de la enfermedad.

Depleción de las células B

La contribución específica de las células B a la inmunopatogénesis de la AR no está bien establecida. Sin embargo, el principal agente empleado para la depleción de estas células es el anticuerpo anti-CD20 (rituximab). Este fue originalmente desarrollado para el tratamiento de linfomas y luego se ensayó en la AR.

La terapia basada en la depleción de las células B con el uso del rituximab se ha investigado ampliamente en los últimos 5 años y las evidencias tempranas de eficacia han sido confirmadas. En la sesión de "Principios terapéuticos no TNF en el tratamiento de la AR" se esbozaron los principales resultados alcanzados con el empleo de este fármaco en el tratamiento de la AR. En el ensayo se utilizó el rituximab con corticosteroides combinado inicialmente con ciclofosfamida. Los protocolos fueron bien tolerados, y apenas se observaron algunos pacientes febriles y con carcinoma de mama. En otros pocos pacientes, los niveles de IgG en suero disminuyeron a niveles no detectables. En general, la experiencia con depleciones repetidas de células B en la AR sugiere que, aproximadamente, el 80% de los pacientes son susceptibles a la continuación del tratamiento.

Terapia contra el receptor de la IL-6

La interleucina 6 (IL-6) es una citocina pleiotrópica que desempeña varias actividades biológicas, como la inducción de la reacción en la fase aguda, la regulación de la respuesta inmune y la promoción de la hematopoyesis [14]. Además, activa los osteoclastos en presencia de su receptor soluble (sIL-6R) [15]. Por estas razones se considera que la superproducción de IL-6 está involucrada con la aparición del factor reumatoideo (FR), la elevación de los niveles de proteínas de la fase aguda, la hipergammaglobulinemia, la trombosis y la destrucción de las articulaciones en pacientes con AR [16]. En ellos se ha observado que los niveles de IL-6 son superiores en el fluido sinovial y en el suero en relación con otros pacientes con otros tipos de artritis [17, 18]. Teniendo en cuenta la importancia de la IL-6 en la AR, Tagaki y colaboradores realizaron experimentos con el modelo experimental de artritis inducida por colágeno, para demostrar por primera vez la relevancia de los anticuerpos neutralizadores de la IL-6 [19]. Otros autores, en diferentes ensayos clínicos han demostrado que es posible la reducción de los signos y síntomas de la AR con el empleo de un anticuerpo monoclonal humanizado dirigido contra la IL-6R [20-23].

En el marco de EULAR 2004 se dedicó un espacio al tema de la IL-6. La conferencia oral, presentada por una experta en el tema de la AR, de la División de Reumatología del Instituto Kennedy en Londres, expuso datos interesantes sobre la eficacia del tratamiento con el empleo de un anticuerpo anti-IL-6 humanizado (MRA, de las compañías Chugai/Roche), durante un estudio clínico aleatorio y controlado por placebo, realizado en Europa y Japón. El ensayo fase II, que incluyó 359 pacientes con AR activa, evaluó las respuestas ante diferentes dosis de MRA administradas, solo y en combinación con metotrexato. Los resultados, evaluados según los criterios ACR20, ACR50 y ACR70, resultaron muy alentadores en cuanto a la eficacia del tratamiento a relativo corto plazo, en especial cuando se combinan el MRA y el metotrexato.

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OP0106 A DOSE ADJUSTMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS NOT OPTIMALLY RESPONDING TO A STANDARD DOSE OF INFLIXIMAB OF 3 MG/KG EVERY 8 WEEKS IS EFFECTIVE: A BELGIAN PROSPECTIVE STUDY

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To analyse the effect of a dose increase in severe rheumatoid arthritis (RA) patients with insufficient clinical response to 3 mg/kg q8 weeks infliximab and to correlate the response with the parameters of the ACR core set. A prospective protocol with infliximab was started for patients suffering from active refractory RA. Patients suffering from active RA despite methotrexate (MTX), were treated with IV infusions of infliximab (3 mg/kg) on week 0, 2, 6 and every 8 weeks thereafter. Based on the expert's clinical judgment of presence or absence of response or loss of response at week 22, patients received a dose increase of 100 mg (1 vial) of infliximab from week 30 on. Assessment using ACR core set for disease activity measures and SF-36 health survey for Quality of life (QOL) was done before infusion at week 0, week 6, and every 2 months thereafter. 511 RA patients were included. The mean disease duration was 12 years and the mean number of previously DMARDs was 3.9. At baseline, CRP was 29.4 mg/L and mean swollen joint count was 15.2. At week 22, 61.4%, 34% and 14.1% of all patients met ACR 20, ACR 50 and ACR 70 criteria, respectively, and 6.1% of patients were in remission. A low SJC at baseline was correlated with improvement at week 22 for ACR 20 ($p<0.06$), ACR 50 ($p<0.06$) and ACR 70 ($p<0.005$). The change in HAQ score between week 0 and 22 was predictive for response at week 54 ($p<0.01$). Based on the rheumatologist's clinical judgment, the dose of infliximab was increased with 100 mg in 22% of the patients. Most baseline values (tender joint count, swollen joint count, health assessment questionnaire, patient and physician global activity, pain) of patients requiring dose increase, were significantly higher (p£ 0.001) than the baseline values of the patients who remained on the indicated dose of 3 mg/kg q8 weeks. Both groups showed a similar improvement for all parameters during the induction therapy (week 0, 2, 6) but there was a clear loss of improvement in the period following the induction period for patients who later on needed a higher dose. Increasing the dose of infliximab with 1 vial from week 30 on could circumvent this partial loss of response. Infliximab administered to patients with active refractory RA in a large outpatient cohort resulted in a significant clinical improvement. A subgroup of patients, who partially lost response during the first 22 weeks of therapy, could regain the response they had obtained initially during the induction of infliximab therapy by adding 100 mg of infliximab to their subsequent doses.

OP0003 CLINICAL OUTCOMES OF A DOUBLE-BLIND STUDY OF ETANERCEPT AND METHOTREXATE, ALONE AND COMBINED, IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS (TEMPO TRIAL), YEAR 2 RESULTS

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To evaluate the relative efficacy and safety of methotrexate (MTX) alone, etanercept alone, and the combination after 2 years of therapy in patients with active RA who have failed previous DMARD therapy other than MTX. In a double-blind randomised study, 682 RA patients were treated with etanercept 25 mg twice weekly (n=223), MTX up to 20 mg/week (n=228), or a combination of etanercept with MTX (n=231) for 2 years. Variables measured include ACR 20, 50, and 70, Health Assessment Questionnaire (HAQ), C-reactive protein (CRP), disease activity score (DAS) and DAS remission (DAS<1.6, DAS rem). The combination of etanercept and MTX was more efficacious than either monotherapy for controlling disease activity as measured by ACR 20, 50, and 70, DAS rem, mean DAS, and mean percentage improvement (% impr) in HAQ and CRP (see table).

Table.

Treatment	ACR 20 (%)	ACR 50 (%)	ACR 70 (%)	DAS (mean)	DAS (% rem)	HAQ (% impr)	CRP (% impr)
MTX	70.6	41.7	20.6	3.0	15.8	35.8	49.2
Etanercept	75.3	53.8*	27.4	2.9	23.3*	38.8	54.2
Combination	86.1 †‡	71.0 †‡	48.5 †‡	2.2 †‡	40.7 †‡	55.8 †‡	75.3 †‡

*p<0.05, E versus MTX; †p<0.05, combination versus MTX; ‡p<0.05, combination versus E

Significantly more patients achieved ACR 50 and DAS remission in the etanercept group compared with the MTX group at 2 years. After 2 years, 40.7% of patients treated with the combination achieved remission compared with 15.8% of patients treated with MTX alone and 23.3% treated with etanercept alone ($p<0.05$). A significantly higher percentage of patients in the combination group remained in the study compared with those in the MTX and etanercept alone groups (71% vs 52% and 61% through 2 years, respectively; $p<0.05$). Fewer patients treated with combination therapy discontinued from the study because of lack of efficacy compared with patients treated with MTX or etanercept (4% vs 14% and 13%, respectively; $p<0.05$). Treatment with etanercept or the combination was well tolerated. No new safety findings were observed and the combination did not result in increased infections after 2 years of therapy. Consistent with year 1 results, the combination of etanercept and MTX was significantly better in reducing disease activity compared with the monotherapies, without an apparent increase in toxicity. These data demonstrated continued and in most cases increasing superiority of combination therapy to monotherapies. Additionally, in several measures of di-sease activity, etanercept is significantly better than MTX after 2 years of therapy.

OP0004 EFFICACY AND ADVERSE EVENTS OF TNFALPHA BLOCKADE IN HUMAN AUTOIMMUNE ARTHRITIS: A ROLE FOR DOWNREGULATION OF TLR EXPRESSION?

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Toll-like receptors (TLR) are critically involved in inflammatory responses and host defense against gram- and gram+ bacteria as well as mycobacteria. Enteroinvasive gram- bacteria as well as specific macrophage subsets expressing the scavenger receptor CD163 play an important role in the pathogenesis of gut and joint inflammation in spondyloarthropathy (SpA). Considering the impressive efficacy as well as the occurence of tuberculosis and infections with gram-positive bacteria after anti-TNFalpha therapy in SpA, we analyzed the expression of TLR2 and TLR4 on specific macrophage subsets in SpA and their modulation by anti-TNFalpha therapy. PBMC were obtained in 9 SpA and 9 patients with rheumatoid arthritis (RA) at week 0, 2, and 6 of infliximab therapy (5mg/kg IV in SpA and 3mg/kg IV in RA), as well as in 9 healthy controls (HC). Expression of TLR2 and TLR4 was analyzed by flowcytometry in CD33+ monocytes and in the CD163+ and CD163- subsets. The number of CD33+ monocytes expressing TLR2 was increased in SpA (92±5%, p=0,007) versus HC (83±8%), with a similar trend in RA (89±8%, p=0,056). TLR4 was increased in both SpA (70±10%, p<0,001) and RA (76±9%) compared to HC (52±7%). Similar results were obtained for the mean fluorescence intensity (MFI). Analysis within the CD33+ population showed that the CD163+ cells had a higher expression of TLR2 (p=0,046) and TLR4 (p<0,001) than their CD163- counterparts, which was confirmed by differences in MFI. Similar results were obtained in SpA and RA. However, the percentage of CD163+ cells within the CD33+ monocytes was not increased in SpA (1±0%) compared to HC (4±4%) or RA (8±7%), indicating that the increased expression of TLR2 and TLR4 on SpA monocytes is not due to a selective increase of CD163+ cells. Indeed, both the CD163+ and the CD163- subset had an increased expression of TLR2 and TLR4 in SpA and RA compared to HC. Treatment in vivo with infliximab in SpA induced a significant decrease of the number of monocytes positive for TLR2 (p=0,002) and TLR4 (p<0,001); these results were confirmed by the MFI. In RA, infliximab treatment decreased TLR4 (p=0,003), with a slight trend for TLR2 (p=0,076). TLR2 and 4 expression on PB monocytes is increased in autoimmune arthritis, especially on the CD163+ subset. Since CD163+ macrophages play a role in SpA pathogenesis and treament with infliximab induced a downregulation of TLR2 and TLR4 expression which was more pronounced in SpA than in RA, the TLR pathway might relate to both the efficacy and the infectious adverse events of TNFalpha blockade in autoimmune arthritis.

OP0040 INCIDENCE RATES OF TUBERCULOSIS IN PATIENTS WITH RHEUMATOID ARTHRITIS OR ANKYLOSING SPONDYLITIS IN COMPARISON WITH THE GENERAL POPULATION

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Background rates of adverse events are important in interpreting the observed rates of these events in rheumatic disease patients treated with DMARDs and biologic therapies. To determine if the incidence rates of TB in RA and AS patients are higher than those in the general population. This was a retrospective cohort study based on the General Practice Research Database (GPRD) of the United Kingdom between 1994 and 2001. The study cohorts included 26,948 patients with RA, 3,262 patients with AS, identified by the Oxford Medical information System (OXMIS) codes or Read Codes consistent with RA or AS. The general population includes >3.3 million patients without rheumatic diseases and/or any other forms of arthritis. All patients aged 15-79 were included in the analysis. Newly diagnosed TB cases during the follow-up period were identified by OXMIS codes or Read Codes. Incidence rate ratios (IRR) for RA and AS, compared with the general population, were calculated by using Poisson regression to adjust for age and sex distribution. Effects of potential risk factors, including history of HIV/AIDS and use of immuno-suppressants and antiviral agents, were also investigated. The table shows age -and sex- specific TB rates in RA, AS, and general populations. The crude incidence rates (number of cases per 100 000 patient-years) were 23 for RA, 19 for AS, and 12 for the general population. After adjusting for age and sex, the IRRs were 1.6 (95% CI: 1.1-2.3) for RA and 1.6 (95% CI: 0.5-4.8) for AS. Poisson regression showed that older age was significantly associated with increased TB risk (IRR = 1.08; 95% CI = 1.07-1.10; p<0.01). RA is associated with a significantly increased risk of TB. The rate observed in AS is apparently greater than that observed in the general population, but not statistically significantly different due to small sample size of the AS cohort. The apparent increase in TB risk observed in RA and AS patients may be important in selection of TNF antagonist therapy.

Table.

Age- and sex-specific incidence rates of TB (per 100,000 pt-yrs)

Age (yrs)	RA Pts Male	RA Pts Female	RA Pts Total	AS Pts Male	AS Pts Female	AS Pts Total	Gen Pop Male	Gen Pop Female	Gen Pop Total
15-34	31	21	23	0	0	0	9	10	10
35-59	22	15	17	27	0	22	12	10	11
60-79	48	21	29	72	0	60	23	17	20
Total	33	18	23	24	0	19	12	12	12

OP0061 INHIBITING THE PROGRESSION OF RADIOGRAPHIC JOINT DAMAGE IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS: COST-EFFICACY ANALYSIS OF INFLIXIMAB AND ETANERCEPT

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Cost effectiveness results may help optimise therapeutic decision making. INF +MTX and ETAN have not been directly compared in head to head trials. However, both treatment strategies have been compared to aggressively dosed MTX monotherapy in patients with early aggressive RA (Smolen, 2003; Bathon, 2000). The patient populations were similar at baseline in numbers of tender and swollen joints, functional disability (HAQ), and radiographic joint damage (assessed by modified Sharp score). Each study followed subjects over 12 months. An important goal of RA medical management is to prevent joint damage; therefore, changes from baseline in radiographic scores with anti-TNF, in comparison with changes observed with MTX monotherapy, provide a means to compare treatments. To conduct a cost efficacy analysis for infliximab (INF) plus methotrexate (MTX) versus etanercept (ETAN) in patients with early rheumatoid arthritis (RA). To compare the efficacy of INF+MTX and ETAN from these two trials, absolute changes from baseline to end of study were calculated. Then the incremental difference in changes were calculated for anti-TNF and its respective MTX monotherapy. The cost for achieving these incremental changes were calculated and compared across trials. The annual cost for INF+MTX with administration assumed 9 (3mg/kg) doses for a 75 kg patient. Cost for ETAN assumed 104 annual 25 mg injections. All assessments assumed treatment in Europe. Italy was selected as the base case because the prices are nearly equivalent for the two anti-TNF therapies. Additional analyses were performed for other European countries. The induction year average cost of INF+MTX in Italy is €13,446 compared to €13,267 for ETAN monotherapy. The erosion progression score was 2.97 for MTX compared to 0.31 for INF+MTX; it was 0.9 for MTX compared to 0.4 for ETAN. The absolute radiographic changes over 12 months and the incremental costs to achieve the decrease in disease progression are shown. The drug and administration costs for INF and ETAN vary across European markets. In Italy where anti-TNF agents cost nearly the same, the cost for the avoided progression in disease is lower for INF+MTX for erosion and TSS and nearly equivalent for JSN scores. Analyses for countries where annual costs of ETAN are lower than INF+MTX had similar findings. A one way sensitivity analysis showed that the annual cost of INF+MTX would have to be five times more than ETAN before the cost per improvement in TSS approximated that shown by ETAN. For those countries where annual ETAN costs are higher than INF +MTX with administration, INF+MTX dominates ETAN. Treatment with INF+MTX is more cost-effective than ETAN in patients with early aggressive RA, as regards alteration in the progression of radiographic joint damage.

References: Smolen *et al*. Ann Rheum Dis 2003; 62:S1:64; Bathon *et al*. NEJM 2000; 343: 1586.

Table.

Score	INF+MTX vs MTX	€/ improvement	ETAN vs MTX	€/ improvement
Erosion change	2.66	5055	0.5	26 534
JSN change	0.52	25 858	0.5	26 534
TSS change	3.28	4099	0.6	22 112

OP0062 ASSESSMENT OF FUNCTIONAL STATUS AMONG PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS IN A DOUBLE-BLIND TRIAL OF ETANERCEPT AND METHOTREXATE, ALONE AND COMBINED (TEMPO TRIAL)

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Previous studies have shown that etanercept improves functional status among either methotrexate (MTX)-naïve or DMARD-refractory patients with active rheumatoid arthritis. To evaluate the impact of etanercept, MTX, and the etanercept + MTX combination on patient's functional status among patients with active rheumatoid arthritis. HAQ was administered at baseline, and at regular intervals for 1 year in a double-blind, parallel-group, 52-week study of 682 patients at 92 centers in Europe, Israel, and Australia. Patients were randomly assigned to etanercept 25 mg twice weekly (N=223), MTX up to 20 mg/week (N=228), or etanercept + MTX (N=231). Mean percent change from baseline in HAQ scores were analyzed. Average area under curve minus baseline (AUCMB) was calculated for HAQ Disability Index score and the 8 HAQ categories. AUCMB was analyzed using analysis of variance (ANOVA). The analyses were implemented for the intent-to-treat population using the last-observation-carried-forward technique for missing data. The patient population was predominantly female (77%) and white (98%), with a mean age of 52.9 years and disease duration of 6.6 years. At baseline, HAQ (MTX 1.7, etanercept 1.8, etanercept + MTX 1.8) scores were comparable among the 3 treatment groups. At week 52, mean percent improvement in HAQ scores were 36%, 39% and 56% in the MTX, etanercept, and combination groups, respectively. The mean percent improvement in HAQ was significantly higher ($p<0.01$) for the combination group compared with either monotherapy. The average AUCMB improvement in HAQ scores for patients in the combination group (0.8) was also significantly ($p<0.05$) higher compared with patients in the etanercept (0.6) or MTX (0.6) alone groups. At week 52, 77%, 77%, and 86% of patients had a clinically meaningful improvement in HAQ disability score (0.22 or higher) in the MTX, etanercept, and combination groups, respectively. The impact of treatment on restoring normal function (HAQ <0.5) was also assessed. At week 52, 34%, 34%, and 44% of patients had a HAQ < 0.5 in the MTX, etanercept, and combination groups, respectively. Both of the above proportions were significantly ($p<0.05$) higher for the combination group compared with either monotherapy. Analysis of the 8 HAQ categories supported the overall results. Patients in the combination group had significantly greater improvement in HAQ Disability Index compared to the patients in the MTX or etanercept groups. Significantly ($p<0.05$) greater proportion of patients in the combination group were restored to normal function (HAQ<0.05) compared with patients in MTX or etanercept group.

References: Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21:271-92.

Table.

Change From Baseline in HAQ Categories Based on Average AUCMB (Week 52)

HAQ Category	MTX	Etanercept	Etanercept+MTX	Statistical Summary*
Activities	0.5	0.6	0.8	A,b
Arising	0.7	0.7	0.8	a
Dressing	0.6	0.7	0.9	A,B
Eating	0.6	0.7	0.9	A,B
Grip	0.5	0.7	0.8	A
Hygiene	0.5	0.5	0.7	A,b
Reaching	0.5	0.6	0.8	A,B
Walking	0.5	0.4	0.7	A,B

*a,A: combination vs. MTX $p<0.05$, $p<0.01$; b,B Combination vs. ETN, $p<0.05$, $p<0.01$

OP0063 CHANGES IN QUALITY OF LIFE OVER ONE YEAR: DATA FROM 2,830 PATIENTS WITH INFLAMMATORY ARTHROPATHIES TREATED WITH DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS), INCLUDING TNF-BLOCKING AGENTS

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Economic evaluation has become increasingly important when governments decide on access to new, effective, but costly medications. Such analyses require access to high quality data on changes in health related quality of life (utility scores). The aim of this analysis was to examine the performance of SF-6D in patients with inflammatory arthropathies receiving therapy with DMARDs and biological agents in a longitudinal observational study. The NOR-DMARD study includes consecutive patients with inflammatory arthropathies in five hospitals in Norway, starting with DMARD regimens. The register is about 85% complete. As of 1st December 2003, 2,830 patients (Mean (SD) age 52.0 (14.8) yrs, 65.4% females, mean disease duration 8.8 (10.1) years) had been included, with the following diagnoses: RA 1 887, psoriatic arthritis (PA) 438, ankylosing spondylitis (AS) 164, juvenile idiopathic arthritis (JIA) 94, other 247. Exposure to regimens were as follows (% out of 2,830): TNF-blocking agents (TNF) 16.2%, methotrexate montotherapy (MTX) 38.3, leflunomide monotherapy (LEF) 10.8, sulphasalazine monotherapy (SASP) 14.2, other monotheapies (MONO) 11.2, and other combination regimens (without TNF-blockers) (COMBO) 9.3. Patients were assessed with core measures of disease activity, including SF-36, MHAQ and VAS of pain and fatigue at baseline, after 3, 6, and 12 months. Health state utilities were calculated from SF-6D on the basis of a validated algorithm (1). The utility assigns the value zero to death and 1.0 to perfect health. Utilities at start of therapy (baseline) and the changes from baseline after 3, 6 and 12 months are shown in the table across the six major groups of treatment regimens (last observation carried forward to replace missing values when patients were withdrawn). The number of patients exposed to therapy in the 3, 6 and 12 -month follow- up periods was 2 517, 2 264 and 1 658, respectively. Changes utility score in the patients receiving TNF-blocking agents were 0.079/0.079/0.071 in RA, 0.130/0.145/0.176 in AS, 0.108/0.138/0.165 in PA, 0.109/0.092/0.05 in JA and 0.130/0.128/0.115 in other arthropathies after 3/6/12 months. In the entire group of patients changes in SF-6D after 3, 6 and 12 months correlated moderately to substantially to changes in MHAQ (r=-0.53, -0.57, -0.54), VAS pain (r=-0.48, -0.50, -0.49), VAS fatigue (r=-0.41, -0.41, -0.41), patient global (-0.50, -0.52, -0.51), investigator's global (-0.34, -0.36, -0.37) and to DAS (-0.43, -0.45, -0.44). Correlations were similar in analyses restricted to patients with RA. SF-6D offers a useful tool for calculation of health state utilities. Utilities from the NOR-DMARD database express the benefits of various therapies in routine use (effectiveness) rather than benefits in optimal trial situations (efficacy). These NOR-DMARD data have a considerable potential for economic evaluation of routine therapies for rheumatic diseases when data on healthcare utilization and changes in work disabilities have also been analyzed.

References: Brazier J, Roberts J, Deverill M. The estimation of a preference based measure of health from the SF-36. J Health Econ. 2002; 21:271-92.

Table.

Utilities (baseline and changes) across treatment groups

	TNF	MTX	LEF	SASP	MONO	COMBO
Baseline	0.561	0.587	0.580	0.610	0.571	0.581
Change 3 m	0.091	0.047	0.033	0.033	0.043	0.041
Change 6 m	0.094	0.055	0.031	0.058	0.044	0.048
Change 12 m	0.091	0.052	0.030	0.048	0.041	0.049

OP0090 LONG TERM OBSERVATION OF BIOLOGICS IN GERMANY-RISK OF TREATMENT TERMINATION

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: To investigate the long-term safety, effectiveness and costs of biologic therapies in rheumatoid arthritis, the German long-term observation study of biologic therapies (RABBIT) in rheumatoid arthritis (RA) was initiated in May 2001. The data of this study were used to examine the probability of treatment termination within the first 12 months after start of treatment. Since May 2001, patients with RA and a new prescription of Etanercept (ETA), Infliximab (INF), Anakinra (since January 2003) or Adalimumab (since September 2003) as well as control patients have been consecutively enrolled in 144 rheumtological units. The control group consists of RA patients with a change of treatment with disease modifying antirheumatic drugs (DMARDs, no first prescription). Follow-ups were done after 3,6, and 12 months and recorded on clinical data forms and patient questionnaires. Kaplan-Meier method and log rank test were applied to compare the probabilities of treatment termination. Only subgroups with a size greater than 100 patients were included in the analysis. As of May 2003, 1295 patients had been enrolled. Among them, 435 were under Etanercept, 298 under Infliximab, 59 under Anakinra and 495 were control cases. In September 2003, 6 (12) months data were available for 80% (53%) of the patients. Nearly half of the ETA patients had no concomitant DMARD therapy (ETA mono) but 33% were additionally treated with Methotrexate (MTX), 9% with Leflunomide (LEF) and 11 % with other DMARDs. For INF the figures were 11% (mono), 64% (MTX), 15 % (LEF), 10 % (other DMARD). Most of the control patients were treated either with LEF and MTX in combination (LEF & MTX) (23%), LEF mono (22%) or MTX mono therapy (21%). As expected, patients under biologics were more severely ill than control patients (e.g. mean disease activity score (DAS28) at baseline: 6.2 (ETA), 6.0 (INF), 5.6 (LEF & MTX), 5.5 (LEF) and 5.2 (MTX)). But interestingly the overall treatment termination rates in the anti-TNF groups did not differ significantly from the LEF termination rates in both LEF subgroups (table). On the other hand, in patients under MTX mono therapy the treatment continuation was higher, likely due to differences in patient case mix (shorter disease duration, lower disease activity at baseline, less previous treatment failures). Treatment termination because of an adverse drug reaction was more frequent under INF (18% in 12 months) than under ETA (11%) whereas no significant differences were found in respect to termination because of inefficacy (17% INF, 16% ETA). Both reasons together were given in 3% and 2%, respectively. We observed similar treatment continuation rates under biologics and under conventional DMARD combination therapy or Leflunomide. Treatment cessation seems to be more frequent in real practice than in clinical trials.

References: Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21:271-92.

Table.

Utilities (baseline and changes) across treatment groups

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Change 6 m	0.094	0.055	0.031	0.058	0.044	0.048
Change 12 m	0.091	0.052	0.030	0.048	0.041	0.049

OP0102 HALTING OF RADIOGRAPHIC PROGRESSION IN PATIENTS WITH RHEUMATOID ARTHRITIS: EXPERIENCE FROM THE TEMPO TRIAL

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In the TEMPO study, the combination of etanercept and methotrexate (MTX) significantly inhibited the progression of structural damage as assessed by radiography, compared with etanercept or methotrexate alone in patients with active rheumatoid arthritis (RA). Additional analyses including cumulative probability plots, secondary radiographic endpoints, and various sensitivity analyses are summarized here. This was a double-blind, parallel-group, multinational study in 682 patients 642 of whom were included in the radiographic analysis. All films were scored by 2 of 3 readers blinded for film sequence, treatment and patient identifiers. The inter- and intrareader correlation of read scores as measured by Intraclass Correlation Coefficient (ICC) was high, ranging from 0.85 to 0.98 and 0.90 to 0.99, respectively. The average scores of the readers were used for the analysis. The primary radiographic endpoint was the annualized change from baseline in van der Heijde-modified total Sharp scores (TSS) at 1 year. Secondary radiographic endpoints included the change from baseline in total erosions, joint space narrowing (JSN), TSS changes <=0.5, 3.0, and smallest detectable difference (SDD; 6.2) and change from baseline at 6 months. Cumulative probability plots, a presentation that provides comprehensive treatment comparisons in clinical trials, along with sensitivity analyses (last observation carried forward [LOCF], valid-for-efficacy [VFE], and completer populations, and analysis based on all 682 patients) and a mixed-model approach were used to confirm primary analysis results. Probability plots of radiographic data clearly illustrated that the combination of etanercept and methotrexate was more effective at inhibiting joint damage than either treatment alone across the entire range of disease progression during the study. The percentage of patients with no progression was significantly higher in the combination or etanercept alone groups compared with the MTX-alone group (Table 1). Statistically significant differences between the groups were already present after 6 months of follow-up. The results of various sensitivity analyses and a mixed-model approach confirmed the results of the primary analysis. Various statistical analyses of TEMPO radiographic data confirmed that the combination of etanercept and MTX resulted in significantly better radiographic outcomes compared with either monotherapy alone. A significant advantage of etanercept alone over methotrexate alone to inhibit joint damage progression was also confirmed. Moreover, these results validate the use of probability plots to visualize treatment differences in radiographic data from clinical trials.

Table.

Percentage of patients with No Progression (TSS<=0.5, 3.0 and SDD) at 1 year

	MTX (n=212)	Etanercept (E) (n=212)	Combination (C) (n=218)
TSS<= 0.5	57.1	67.9*	79.8 †, ‡
TSS<= 3.0	77.4	87.3 §	94.5 †, ‡
TSS<= SDD	88.2	95.8 §	97.2 †

*p<0.05 E vs MTX, †p<0.01 C vs MTX, ‡p<0.01 C vs E, §p<0.01 E vs MTX

OP0103 PATIENT PREFERENCES FOR TREATMENT OF NEWLY DIAGNOSED RHEUMATOID ARTHRITIS

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To determine the preference for treatment of patients with newly diagnosed rheumatoid arthritis (RA). The BeSt trial is a multicentre, randomised, single blinded trial in 508 patients with newly (<2 years duration of signs and symptoms) diagnosed RA (ACR 1987 criteria: =6/66 swollen joints, =6/68 tender joints, ESR =28 mm/hr or VAS global health =20 mm) who have not previously received disease modifying antirheumatic drugs (DMARDs). Patients were randomised to one of four different treatment strategies: Group 1 (n=125): Sequential monotherapy starting with methotrexate (MTX) up to 25 mg/week, next treatment step sulphasalazin (SSA), followed by leflunomide; Group 2 (n=122): Step-up therapy from MTX, next step add SSA, then add hydroxychloroquine; Group 3 (n=133): Step-down therapy from MTX + SSA + prednisone 60 mg tapered to 7.5 mg; and Group 4 (n=128): Treatment with MTX and infliximab 3 mg/kg. Adjustment in treatment for each strategy was dictated by three monthly calculations of the disease activity score (DAS44), with the goal of achieving a DAS44 =2.4. All patients were asked to complete a questionnaire about their experiences and preferences since the start of treatment. A total of 357 patients returned a completed questionnaire. More patients in group 4 (75%) found that their general health had much or very much improved from their treatment (percentages for groups 1, 2 and 3 were 56%, 60% and 50%, respectively. More patients in groups 3 (80%) and 4 (86%) said that they had improved quickly (percentages for groups 1 and 2 were 51% and 57%, respectively). The percentage of patients indicating that their current health status and treatment would be acceptable for the next year was lowest in group 3 (75%, see table). Group 3 had the highest percentage of patients who, irrespective of treatment strategy, disliked taking prednisone (49%). Given the choice, 81% of patients in group 4 would prefer the same treatment they received after randomisation. Overall, 44% of patients in the BeSt trial, irrespective of treatment strategy, would now prefer treatment with 'the newest intravenous (iv) antirheumatic drug' (breakdown by group: 41%, 30%, 22%, and 81%, respectively). A small percentage of patients (1% in groups 1, 2 and 3; 4% in group 4) objected to having to come to the hospital to receive iv treatments. The majority of patients who participated in the BeSt trial and responded to the questionnaire indicated that they had benefited greatly by the treatment, especially those in group 4 (infliximab with MTX). Many patients in group 3 expressed an aversion to taking prednisone, which is reflected in the fact that fewer patients in group 3 than in group 4 would choose their allocated treatment. Most patients prefer 'the newest drug', and do not object to having to come to the hospital for iv treatment.

Table.

	Percentages of patients designating preference			
Patient preference	Group 1 Monotherapy n=78	Group 2 Step-up therapy n=79	Group 3 Combination n=101	Group 4 Infliximab n=99
Initial treatment improved general health much or very much (%)	56	60	50	75
Finds current health status and treatment acceptable for the next year (%)	87	86	75	87
Objects to coming to hospital for iv treatment (%)	1	1	1	4
Objects to taking prednisone (%)	15	22	49	11
Would now choose the treatment that was received following randomisation (%)	36	30	41	81

OP0105 EFFICACY AND SAFETY OF ADALIMUMAB (HUMIRA®) IN EUROPEAN CLINICAL PRACTICE: THE REACT TRIAL

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Patient management, patient characteristics, and treatment outcomes observed in randomized, controlled clinical trials do not always reflect real-life clinical practice. Large, open-label trials can be used to confirm controlled trial data in real-life clinical conditions. To evaluate the efficacy and safety of adalimumab, a fully human, anti-TNF monoclonal antibody, in an open-label, multinational rheumatoid arthritis (RA) trial. The Adalimumab Research in Active RA (ReAct) trial is an open-label, multi-center, multinational, Phase IIIb study conducted primarily in Europe. Patients with moderate to severely active RA who had an inadequate response to standard antirheumatic therapy were treated with adalimumab 40 mg subcutaneously every other week in addition to their pre-existing but inadequate therapies. Efficacy and safety were assessed at weeks 2, 6, and 12. Efficacy assessments included ACR and EULAR response criteria, and the individual components thereof. Beyond week 12, patients were allowed to continue on adalimumab therapy until commercially available, with follow-up visits every 8 weeks. The trial is ongoing. Efficacy data at 12 weeks was available for 2008 patients from more than 400 sites in 11 participating European countries as of November 2003. Patient baseline characteristics and disease severity scores were (mean) age = 53 years, duration of disease = 11 years, DAS28 =6.0, and HAQ =1.6. Of the 2008 patients, 872 had complete information on prior and concomitant therapy at the time of this analysis. Of these, 18% (n=164) had previously taken one or more biologic DMARD, and 72% (n=630) were taking at least 1 concomitant DMARD, most commonly, methotrexate. Results at week 12 are presented in the table below for the overall population, and those patients with and without prior biologic therapy. In the overall population, median TJC and SJC were each 3 at week 12, a change of –10 and –7, respectively. HAQ scores dropped to 1.0, with 25% of patients with a HAQ score of <0.5. DAS28 scores dropped 2.1 units, with 24% of patients achieving remission (DAS28 score <2.6). Mean PPD positivity at baseline was 11%, with a range of 2-22% across the 11 countries. The safety profile (SAEs) of adalimumab in this trial was consistent with the overall safety database from the pivotal trials. No new alerting safety signals were observed. Patients with RA receiving adalimumab in a real-life, clinical setting consistently experienced substantial reductions in signs and symptoms of their disease. These results compare favorably with results from adalimumab randomized, controlled trials. Adalimumab also demonstrated similar high efficacy in patients who had previous biologic experience.

Table.

Efficacy measurement at week 12	Overall Population N=2008	No Prior Biologic N=708	Prior Biologic N=164
ACR20 (%)	67	67	59
ACR50 (%)	39	35	32
ACR70 (%)	17	14	12
Moderate EULAR Response (%)	82	79	79
Good EULAR Response (%)	34	32	24
Change HAQ (mean)	-0.49	-0.43	-0.41
Change DAS28 (mean)	-2.1	-1.9	-2.0

OP0001 A COMPARISON OF CLINICAL AND RADIOLOGICAL OUTCOMES OF FOUR TREATMENT STRATEGIES FOR EARLY RHEUMATOID ARTHRITIS: RESULTS OF THE BEST TRIAL

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To compare the clinical and radiological outcomes of four different treatment strategies for early rheumatoid arthritis (RA). The BeSt trial is a multicenter, randomised, single blind trial in 508 patients with newly (<2 years duration of signs and symptoms) diagnosed RA (ACR 1987 criteria: =6/66 swollen joints, =6/68 tender joints, and ESR =28 mm/hr or VAS global health =20 mm) who have not previously received DMARDs. Patients were randomised to one of four treatment strategies: Group 1 (n=125): Sequential monotherapy starting with methotrexate (MTX) up to 25 mg/week, next treatment step sulphasalazin (SSA), followed by leflunomide; Group 2 (n=122): Step-up therapy from MTX, next step add SSA, then add hydroxychloroquine; Group 3 (n=133): Step-down therapy from MTX + SSA + prednisone 60 mg tapered to 7.5 mg; and Group 4 (n=128): Treatment with MTX (7.5 mg/wk for 2 weeks, then 15 mg/wk) and infliximab (3 mg/kg at week 0, 2, and 6, then every 8 weeks, doses increased or reduced to zero depending on disease activity score (DAS44)). Adjustment in treatment for each strategy was dictated by three monthly calculations of DAS44, with the goal of achieving DAS44 =2.4. Clinical outcomes, DAS44, and health assessment questionnaires (HAQ) were obtained by blinded assessors. Sharp/van der Heijde radiological scores (SHS) were performed by two independent blinded physicians. At baseline there were no significant differences in patient characteristics between the groups. After 3 months, the average HAQ reduction was 0.4 and 0.3 in group 1 and group 2, respectively, and 0.8 and 0.7 in group 3 and group 4, respectively. After one-year of follow-up, the reduction in HAQ was 0.7 in groups 1 and 2 and 0.9 in groups 3 and 4 (p= 0.04). Median SHS-progressions after 1 year of follow-up were 2.0, 2.5, 1.0, and 0.5 for groups 1-4, respectively (p<0.001). In group 1, 27% of patients did not show any radiological progression (values for groups 2-4 were 29%, 37%, and 46%, respectively [p=0.007]). There was no significant difference in the number of dropouts or in the incidence of adverse events and serious adverse events (SAEs) between the groups. In early RA patients who received three monthly treatment adjustments intended to reach a DAS44 =2.4, initial treatment with combination therapy and initial treatment with infliximab plus MTX resulted in significantly greater and more rapid reduction in HAQ as well as in significantly less radiological damage than sequential monotherapy or step-up therapy.