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ASOCIACIÓN DE REUMATÓLOGOS DE PUERTO RICO

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Retos en el diagnóstico temprano de la artritis reumatoide

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La artritis reumatoide (AR) es una enfermedad autoinmune que produce un proceso inflamatorio crónico. Su origen es desconocido y su manifestación más común es en las articulaciones. Por ser una enfermedad sistémica, puede estar también asociada a síntomas constitucionales y con frecuencia puede haber manifestaciones extra articulares. La AR es más común entre las mujeres (3,5 veces más frecuente) y, aunque puede expresarse a cualquier edad, la mayor incidencia es entre la cuarta y quinta década de vida.

Importancia del diagnóstico temprano

Un diagnóstico temprano y un tratamiento apropiado con medicamentos modificadores de la enfermedad pueden evitar el daño estructural permanente en las articulaciones. Esta es la estrategia más eficaz para disminuir el riesgo de incapacidad y pérdida de la productividad.

Un diagnóstico tardío y un tratamiento subóptimo pueden tener consecuencias devastadoras para los pacientes. Las consecuencias de un pobre control médico a nivel personal, no sólo serían la pérdida de función física sino también dolor crónico, depresión, impacto negativo en calidad de vida, incapacidad de mantener un empleo e, incluso, una mortalidad temprana.

Los pacientes que sufren de AR tienen una incidencia más temprana de enfermedad coronaria, mayor incidencia de ciertas malignidades como linfoma y pueden sufrir serias complicaciones como vasculitis, compromiso pulmonar y renal. Si a esto añadimos los costos indirectos que manejar las complicaciones asociadas a la enfermedad, como reemplazos articulares, hospitalizaciones y visitas a sala de emergencia, podemos entender el impacto socioeconómico que significaría no tratar temprano y efectivamente a los pacientes de AR.

Los pacientes con AR, una vez identificados, deben recibir un tratamiento especializado para el manejo preventivo y la vigilancia de complicaciones potenciales asociadas, tanto con el curso natural de la enfermedad como con las terapias farmacológicas utilizadas.

Sin embargo, los pacientes con un cuadro clínico temprano de AR no presentan los hallazgos que comúnmente asociamos con la enfermedad, como las deformaciones articulares, las erosiones en radiografías o los nódulos reumatoides, que son más comunes en pacientes con enfermedad establecida, sea moderada o severa. Es por esto que destacamos cómo evaluar a un paciente en la oficina de su médico primario con síntomas que podrían sugerir AR. Estos hallazgos y molestias en un paciente que está desarrollando AR o en un estado temprano de la enfermedad pueden ser poco específicos, por lo que es importante darle énfasis a su historia clínica y realizar un examen físico cuidadoso.

Historial del paciente

Es imprescindible tomar un historial detallado que incluya la duración de los síntomas, si el desarrollo fue abrupto o gradual, la localización del dolor o patrón de las articulaciones afectadas, la presencia de hinchazón, enrojecimiento o calor a nivel articular y la duración del entumecimiento matutino. Debemos preguntar sobre síntomas constitucionales: fiebre, malestar general, pérdida de peso y cansancio.

Parte del historial debe dirigirse a descartar enfermedades que puedan causar una artritis inflamatoria, siendo las más comunes: artritis psoriásica, síndrome viral previo al inicio de los síntomas, enfermedades inflamatorias del intestino, lupus sistémico y osteoartritis erosiva. Es importante preguntar sobre historial familiar de AR y si

el paciente es fumador, ya que estos factores afectan el pronóstico.

La presencia de síntomas por menos de 6 semanas nos debe hacer pensar en una enfermedad viral que causa un cuadro artrítico; por otro lado, mientras mayor sea la duración de los síntomas, más probable es que sea un cuadro de AR. En pacientes con síntomas de poca duración lo indicado es una evaluación básica; si hay historial de exposición a niños con enfermedades febriles, medir títulos de parvovirus; considerar seroconversión a HIV o hepatitis, si existen factores de riesgo. Un cuadro agudo de hepatitis C puede producir dolor articular, marcadores de inflamación elevados y un factor reumatoideo positivo.

Síntomas

El manejo inmediato de los síntomas debe ser conservador con un seguimiento a corto plazo. Un paciente severamente incapacitado se debe referir cuanto antes al reumatólogo, y de ser posible, con una conversación para agilizar este paso.

El desarrollo de los síntomas de AR suele ser lento y a lo largo de semanas, pero hay casos de presentación aguda y dramática. El patrón de afectación articular usual es simétrico y poliarticular, con predilección de las articulaciones de metacarpo, falanges e interfalangeales proximales, así como de muñecas.

Con el avance de la enfermedad puede haber compromiso de las articulaciones más grandes como rodillas, tobillos y hombros. En raras ocasiones, puede haber compromiso de una sola articulación con hinchazón, dolor al movimiento, enrojecimiento y calor a la palpación. En estos pacientes se debe considerar la posibilidad de gota, pseudogota y, sobre todo, artritis séptica.

Ayuda mucho saber si hay rigidez o entumecimiento matutino. Generalmente los pacientes dicen que necesitan poner las manos bajo agua caliente o tomar una ducha caliente en la mañana para recuperar un poco de movilidad. El saber cuánto tiempo toma volver a moverse con facilidad nos puede dar una idea más clara sobre la rigidez matutina.

Examen físico

El examen físico debe ser completo y con énfasis en las articulaciones. Siempre debemos estar atentos a hallazgos que puedan sugerir otra posible explicación para los síntomas. El examen de las articulaciones es la parte que más información debe proporcionar. El hallazgo más significativo es la hinchazón articular simétrica, particularmente MCP y PIP (articulaciones metatarsofalángica y proximal interfalángica) y las muñecas.

La hinchazón asociada a sinovitis se siente mullida al apretar la articulación y el paciente siempre sentirá dolor con la compresión. Cuando hay osteoartritis la sensación al examinar la articulación es de hinchazón firme, de carácter óseo. También es fácil detectar sinovitis en las muñecas, los codos y las rodillas.

La detección de sinovitis en el hombro y la cadera es más difícil, siendo allí más común hallar dolor y limitación de movimiento. La rodilla, aún siendo una articulación grande, se afecta con frecuencia y es común que haya una efusión por sinovitis. Con el avance de la enfermedad, las articulaciones de los tobillos y las metatarsofalanges también se ven afectadas. De acuerdo al grado de hinchazón y al tiempo de duración de los síntomas, se puede apreciar pérdida de movimiento.

Además, se debe buscar claves de compromiso sistémico como pérdida de peso, escleras enrojecidas, boca y ojos secos, eritema palmar (manifestación temprana), estertores pulmonares, hinchazón de las piernas, entre otros.

Cuando el diagnóstico diferencial incluye artritis séptica, la articulación debe ser drenada cuanto antes y el líquido enviado para análisis. De observarse estos hallazgos en el examen físico el paciente se deberá referir al especialista lo antes posible.

Comentario

Afortunadamente, disponemos de nuevas alternativas terapéuticas que ayudan a manejar los síntomas de esta enfermedad. De esa manera se le puede detener y evitar así el daño severo e incapacitante a las articulaciones. G

Biosimilares para el tratamiento de la artritis reumatoidea

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Los biosimilares son medicamentos que pueden resultar una alternativa para los agentes biológicos tradicionales. Los medicamentos biológicos pueden ser sumamente costosos y los biosimilares son una opción para aquellos pacientes que no pueden cubrir los costos de los medicamentos biológicos.

La introducción de las terapias con agentes biológicos ha mejorado dramáticamente el desenlace de los pacientes con artritis reumatoide. Los primeros agentes biológicos tienen patentes que están próximos a expirar, lo que ha llevado al desarrollo de nuevas versiones de estos agentes biológicos llamados biosimilares. Los agentes biosimilares permiten también mejorar la accesibilidad de los pacientes a estos productos.

¿Qué es un agente biosimilar?

Un agente biosimilar es un producto bioterapéutico, que es similar en calidad, seguridad y eficacia a un agente bioterapéutico con licencia o patente.

La similaridad se define como la ausencia de diferencias relevantes en los parámetros de interés. Estos productos deben ser desarrollados bajo estrictos parámetros según lo establecido por las autoridades regulatorias, como la Agencia Europea de Medicina (EMA) o la Agencia de Alimentos y Medicamentos de los Estados Unidos (FDA). Estos requisitos estrictos permiten que el producto biosimilar cumpla con los criterios de seguridad, pureza y potencia (FDA) o con los criterios de calidad, seguridad y eficacia (EMA).

Actualmente, existen algunos productos que son considerados biosimilares para tratamiento de artritis reumatoide pero que no cumplen con los criterios establecidos por la EMA y la FDA. Estos productos son considerados copias no biosimilares ya que no cumplen con los estándares establecidos por las agencias antes mencionadas. Estos fármacos están disponibles en distintos países del mundo bajo diferentes nombres o marcas.

Los médicos debemos estar bien informados sobre la diferencia que hay entre un verdadero biosimilar que cumple con los criterios EMA/FDA y las copias de biológicos.

Diferencia entre biosimilares y biológicos

La pregunta clave aquí debe ser: ¿son realmente las diferencias entre los biosimilares y los biológicos clínicamente significativas?

Dada la complejidad en la producción de estos fármacos, no es posible que un biosimilar sea exactamente igual al producto de referencia. En términos generales, la FDA y la EMA exigen ciertas características particulares para que estos productos sean aprobados. Entre ellas están la secuencia de aminoácidos primaria, la potencia, la ruta de administración y las modificaciones post translacionales, que deben ser muy semejantes al producto de referencia.

Algunos de los productos que actualmente son objeto de estudios de investigación para lograr su aprobación como biosimilares son: rituximab, infliximab y etanercept. Algunos de ellos tienen resultados preliminares que apuntan a que pueden resultar ser extremadamente parecidos a los productos de referencia y así cumplir con los estándares establecidos por la FDA y la EMA.

Rol de los biosimilares en la reumatología

El papel que los biosimilares lleguen a tener en la reumatología va a ser determinado por el grado de confianza que los reumatólogos desarrollen hacia estos productos. Los criterios de la EMA y de la FDA para su aprobación buscan precisamente darle al médico reumatólogo la confianza o seguridad para que pueda prescribir estos biosimilares. Sin embargo, los ahorros que pueden traer estos productos fluctúan entre un 15-30%, lo que es mucho menos de lo esperado si consideramos que la diferencia en costo entre un genérico y un original puede ser de hasta un 80%. Realmente resulta difícil utilizar un producto biosimilar para tener un ahorro mínimo en el producto.

En la actualidad, algunas de las compañías farmacéuticas que producen los biológicos de referencia también se han dado a la tarea de trabajar para producir biosimilares buscando poder continuar compitiendo en este mercado.

Resumen

Es importante que podamos distinguir las diferencias entre un biosimilar y una copia. Para obtener el nivel o categoría de biosimilar, el producto debe cumplir con los estrictos criterios de la FDA y de la EMA.

Se espera que eventualmente estos productos nos conduzcan a un ahorro significativo y, por lo tanto, que un mayor número de pacientes se puedan beneficiar de esta excelente categoría terapéutica. Una vez estén disponibles los biosimilares, es nuestro compromiso como médicos estar al día sobre cualquier información, datos o cambios que surjan en torno a la utilización o a las recomendaciones de estos productos.

Referencias

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2. Schneider, C. Biosimilars in Rheumatology: the wind of change. Ann Rheum Diseases March 2013;vol 72(3):315-318.
3. Roger S, Mikhail A. Biosimilars: opportunity or cause for concer? J Pharm Pharm Sci 2007;10:405-410.

Reumatología pediátrica:
Si no se sospecha, no se diagnostica

Sobre un caso clínico de la rara enfermedad inflamatoria sistémica de inicio neonatal

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Aspectos generales

La enfermedad inflamatoria sistémica de inicio neonatal (conocida también como *NOMID, neonatal-onset multisystem inflammatory disease o CINCA, chronic infantile neurologic cutaneous articular syndrome)* es un desorden congénito sumamente raro.

Se caracteriza por:

- comenzar durante el periodo neonatal,
- con fiebres recurrentes,
- inflamación,
- síntomas cutáneos,
- manifestaciones en las articulaciones,
- dimorfismo facial, y
- compromiso del sistema nervioso central (SNC), que se puede manifestar como meningitis crónica, papiledema bilateral, pérdida de audición sensoneural, retardo mental y/o atrofia cerebral.

Etiología

Las mutaciones en el gen NLRP3 (antiguamente denominado CIAS1), que codifica la criopirina, son la causa de esta condición. La criopirina se asocia a la producción de IL-1 (interleucina 1). Los resultados negativos para mutaciones no excluyen su diagnóstico, ya que solo se encuentran en el 50% de estos pacientes.

Un caso raro en reumatología pediátrica

Caso clínico:
Una paciente de 4 meses, sin problemas perinatales y con fiebre prolongada. Desde su nacimiento mostró erupción en la piel que se diagnosticó como dermatitis, por lo que recibió ocasionalmente esteroides orales, a los que respondió.

A los 2 meses de edad había desarrollado fiebre ocasional. A los 4 meses, la fiebre se volvió persistente, por lo que se le llevó al hospital para evaluación. En el historial los padres refieren una convulsión que se diagnosticó como febril aunque, no tuvo fiebre.

El examen físico mostró una paciente contenta, bien nutrida, en percentil 5 de crecimiento, con fiebre, con erupción eritematosa maculopapular en la piel y con la nariz de sutil apariencia de silla de caballo *(saddlenose)*. El resto del examen fue normal y las pruebas de laboratorio reflejaron un proceso inflamatorio.

Se sospechó NOMID, por lo que se envió material genético a un laboratorio especializado que identificó una mutación en *NLRP3*, lo que da un diagnóstico certero de *NOMID*.

Con el diagnóstico se iniciaron esteroides orales y bloqueador de IL-1, con excelentes resultados.

En este caso, la erupción en la piel desde el nacimiento es lo primero que elevó el índice de sospecha de *NOMID*. El que haya tenido una convulsión sin causa aparente sugirió el compromiso del sistema nervioso central. Además, la fiebre persistente y el muy sutil dimorfismo facial dieron más fuerza a la sospecha de *NOMID*.

Este caso se diagnosticó hace 5 años sin que haya desarrollado ninguna complicación, lo que se atribuye a la intervención temprana. Se trata de la paciente más joven en el mundo que ha sido diagnosticada y con tratamiento inmediato, por lo que se viene evaluando con interés especial (inclusive con la participación de NIH).

Comentario

En este ejemplo de una enfermedad muy rara –que es usualmente diagnosticada cuando ya hay complicaciones– vemos lo importante que es tenerla presente para lograr un diagnóstico temprano, más aún cuando puede haber una muy buena respuesta al tratamiento. G


Moderate to Severe Rheumatoid Arthritis (RA)
The jeans didn’t last.

Because the joints did.

Improving physical function and preventing further joint damage are key goals in managing RA.

Improvement in Physical Function, as measured by HAQ-DI, was greater in patients treated with HUMIRA + MTX vs MTX alone at Year 1, in a clinical study of 619 patients with moderate to severe RA who had an inadequate response to MTX. **Through 5 years of open-label treatment, patients originally treated with HUMIRA maintained improvement in physical function.**[1]

Greater Radiographic Inhibition was achieved in patients treated with HUMIRA + MTX vs MTX alone at Year 1 in the same study, as measured by mean change from baseline in mTSS.[1]

Maintained Inhibition of Structural Damage through 5 years of open-label treatment in the same study. 55% (n=113) of patients originally treated with HUMIRA 40 mg EOW were evaluated at 5 years, with 50% (n=57) showing no progression of structural damage (change in mTSS ≤0). The overall mean change from baseline in mTSS at 5 years for patients originally treated with HUMIRA 40 mg EOW (n=113) was 0.8.[1,2]

HUMIRA specifically targets TNF-α, one of the key cytokines in inflammation.

Indication[1]

Moderate to Severe Rheumatoid Arthritis: HUMIRA is indicated, alone or in combination with methotrexate or other non-biologic DMARDs, for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.

Safety Considerations[1]

Serious Infections: Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include active tuberculosis (TB), reactivation of latent TB, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Malignancies: Lymphoma, including a rare type of T-cell lymphoma, and other malignancies, some fatal, have been reported in patients treated with TNF blockers, including HUMIRA.

Other Serious Adverse Reactions: Patients treated with HUMIRA also may be at risk for other serious adverse reactions, including anaphylaxis, hepatitis B virus reactivation, demyelinating disease, cytopenias, pancytopenia, heart failure, and a lupus-like syndrome.

References: 1. HUMIRA Injection [package insert]. **2.** Data on file, AbbVie Inc.

Please see additional Important Safety Information, including BOXED WARNING on Serious Infections and Malignancy, on the following page.

Please see Brief Summary of full Prescribing Information on last pages of this advertisement.

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Help preserve what matters

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PROFESSIONAL BRIEF SUMMARY
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WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 34 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) and plaque psoriasis (Ps), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.38, 0.91) per 100 patient-years among 7304 HUMIRA-treated patients versus a rate of 0.6 (0.30, 1.03) per 100 patient-years among 4232 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 47 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, and Ps, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, and Ps, the rate (95% confidence interval) of NMSC was 0.7 (0.49, 1.08) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.08, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC and Ps, 3 lymphomas occurred among 7304 HUMIRA-treated patients versus 1 among 4232 control-treated patients. In 47 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC and Ps with a median duration of approximately 0.6 years, including 23,036 patients and over 34,000 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA.

HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 34 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) and plaque psoriasis (Ps), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.38, 0.91) per 100 patient-years among 7304 HUMIRA-treated patients versus a rate of 0.6 (0.30, 1.03) per 100 patient-years among 4232 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 47 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, and Ps, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, and Ps, the rate (95% confidence interval) of NMSC was 0.7 (0.49, 1.08) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.08, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC and Ps, 3 lymphomas occurred among 7304 HUMIRA-treated patients versus 1 among 4232 control-treated patients. In 47 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC and Ps with a median duration of approximately 0.6 years, including 23,036 patients and over 34,000 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA.

Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that JIA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*

Clinical Trials Experience

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC and Ps, the rate of serious infections was 4.6 per 100 patient-years in 7304 HUMIRA-treated patients versus a rate of 3.1 per 100 patient-years in 4232 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 47 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC and Ps that included 23,036 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.22 per 100 patient-years and the rate of positive PPD conversion was 0.08 per 100 patient-years. In a subgroup of 9396 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.07 per 100 patient-years and the rate of positive PPD conversion was 0.08 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.08 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in patients with CD with control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with JIA, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In patients with CD, the rate of antibody development was 3%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 ug/ml. Among the patients whose serum adalimumab levels were < 2 ug/ml (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 ug/ml. Among the patients whose serum adalimumab levels were < 2 ug/ml (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated pediatric patients in the juvenile idiopathic arthritis (JIA) trial were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions and Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

HUMIRA was studied in 171 pediatric patients, 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

A total of 45% of children experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in children receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment, non-serious hypersensitivity reactions were seen in approximately 6% of children and included primarily localized allergic hypersensitivity reactions and allergic rash.

Isolated mild to moderate elevations of liver aminotransferases (ALT more common than AST) were observed in children with JIA exposed to HUMIRA alone; liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment.

In the JIA trial, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of children treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK). Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 patients with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for patients with Ps treated with HUMIRA was similar to the safety profile seen in patients with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps patients, HUMIRA-treated patients had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

Although methotrexate (MTX) reduces the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, and Ps. Concomitant administration of HUMIRA with

FUTURA DOCTORA

¿Por qué estudio Medicina?

Nuria S. García-Ruiz
MD Candidate Class of 2015
Ponce School of Medicine and Health Sciences

En esta época de entrevistas, electivas, exámenes, *resumés* y estrés por la que pasa todo estudiante de Medicina, una de las preguntas más difíciles de contestar es ¿por qué estás aquí?, ¿por qué medicina? Y es que cuando algo te gusta –y te gusta de verdad– explicar por qué lo haces es casi imposible.

Es difícil describir la satisfacción que uno siente al ver los ojos de agradecimiento de una madre o la sonrisa de un paciente al oír "Eso tiene solución". Las "mariposas" que tuve al ver mi primer parto o la emoción que sentí al entrar por primera vez a sala de operaciones, la ansiedad que me dio al coger esa primera sutura, esa primera lágrima que aguanté al darle el pésame a un familiar o esa primera experiencia de cambiarle la vida a un paciente y a mí misma; en fin, ese golpe de adrenalina y satisfacción, todo esto es verdaderamente inexplicable. Sentimientos que motivan, que te hacen crecer, que te hacen un mejor ser humano. Esa necesidad insaciable de interactuar con pacientes, de conocer anécdotas nuevas, historias interesantes y a veces inverosímiles; o la emoción al recibir las gracias, en ocasiones en bolsitas de café o aguacates, que dicen mucho más que un "Estoy agradecido"; o atender a mujeres embarazadas con quienes –aun "con las hormonas a millón", como coloquialmente decimos– creas un vínculo especial sabiendo que durante 40 semanas compartes el cuidado de la vida de su hijo.

Tal vez no todos lo hacen por vocación o por amor, pero los que sí lo hacemos por eso, por ese sentimiento indescriptible, por esa combinación de satisfacción, de felicidad y de adrenalina que solo la medicina nos da, me entenderán cuando digo que la pregunta más difícil de contestar para mí es: ¿por qué estudio Medicina?

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Artritis reumatoide:
Breve discusión sobre opciones de medicina alternativa o complementaria

Especial para *Galenus* - Revista para los médicos de Puerto Rico -
Condensado de *National Center for Complementary and Alternative Medicine*, de los Institutos Nacionales de Salud (NIH)

La artritis reumatoide (AR) suele mostrar dolor, inflamación, rigidez y pérdida de función articular, y la terapia médica convencional es altamente efectiva.

La información científica sobre opciones de medicina complementaria ha sido siempre limitada. Por ello, los Institutos Nacionales de Salud (NIH) promueven su estudio en el Centro de Medicina Complementaria y Alterna. Algunos de estos tratamientos buscan reducir la inflamación o el dolor. Este resumen discute algunas alternativas terapéuticas de mente y cuerpo, de nutrición y otras que son evaluadas.

Puntos claves

- Los actuales tratamientos convencionales son altamente efectivos en disminuir o frenar el daño permanente a las articulaciones en AR;
- No se debe reemplazar la terapia médica convencional por prácticas o por productos que no han sido científicamente probados;
- En general, no hay suficiente evidencia que pruebe que cualquier opción complementaria sea de beneficio en artritis reumatoide;
- Algunas prácticas de "mente y cuerpo" y de nutrición podrían ayudar a manejar los síntomas y ser un complemento adicional a los tratamientos convencionales en AR, pero no hay estudios concluyentes ni suficiente evidencia para ello;
- Algunas prácticas complementarias –en particular suplementos nutricionales– pueden producir efectos secundarios que interactúen con la medicina tradicional, o viceversa. El término "natural" no significa "seguro". En particular, la hierba *tripterygium wilfordii (thunder god vine)* puede tener serios efectos adversos; y
- Es importante estar informados sobre las alternativas complementarias que los pacientes puedan utilizar, para así poder ofrecerles un cuidado seguro.

Tratamiento para artritis reumatoide

Es importante un diagnóstico temprano para iniciar cuanto antes un tratamiento y poder así evitar un daño permanente a las articulaciones que puede ser progresivo y limitante.
Las alternativas convencionales en AR son:

- Medicamentos modificadores de la enfermedad (DMARDs), que disminuyen la progresión de la enfermedad;
- Modificadores de la respuesta biológica para reducir la inflamación y el daño estructural;
- Medicamentos antiinflamatorios no esteroides (NSAIDs) y corticoesteroides, para reducir la inflamación; y
- Otras opciones incluyen cirugía, terapia física, programas de ejercicio adaptado así como elementos ortopédicos que den soporte o ayuden a disminuir la carga sobre alguna articulación.

También se puede aconsejar a los pacientes con AR a hacer algunos cambios en su modo de vida, como buscar balancear la actividad física con el reposo, tener una alimentación saludable y un peso adecuado, así como disminuir el estrés emocional.

Sobre la evidencia científica de las opciones de la medicina complementaria

La evidencia científica incluye resultados de laboratorio y estudios clínicos en humanos, los que tienen que cumplir las normas científicas que se emplean para los estudios clínicos de revisión y de meta-análisis.

Lo que dice la ciencia

Resumiendo los muchos estudios, se puede concluir que, por lo general, no hay evidencia científica que pruebe que los métodos complementarios puedan ser de beneficio en AR y hay dudas sobre la seguridad de los mismos.

Prácticas de mente y cuerpo

Los estudios clínicos sugieren que algunas formas de prácticas de "mente-cuerpo" tales como la relajación, la meditación, el tai chi o el yoga ayudan a controlar los síntomas en pacientes con AR o que pueden ser de apoyo al tratamiento convencional.

Suplementos nutricionales

Ningún suplemento nutricional ha demostrado beneficios claros en AR. Se debe estudiar aún su interacción con la medicina convencional.

- **Aceites de pescado y ácidos grasos** omega-3: los estudios clínicos en AR han demostrado que pueden aliviar las articulaciones tensas, sobre todo en las mañanas, y que pueden disminuir la dosis necesaria de NSAIDs en cerca del 30% en un periodo de 9 meses. Por otro lado, pueden disminuir la coagulación, lo que puede ser crítico en pacientes con anticoagulantes o con factores de riesgo.

- **Ácido gamma-linoleico** (GLA): es un ácido graso omega-6 que se encuentra en algunas semillas. Se dice que puede reducir la inflamación, pero los estudios aún no son consistentes. Otros estudios más rigurosos sugieren que puede aliviar síntomas y llevar a disminuir la dosis de las medicinas convencionales. Pero puede tener efectos adversos a nivel digestivo e intestinal, y algunos preparados con alcaloides de pirrolisidina pueden dañar el hígado.

- **Tripterygium wilfordii** *(Thunder god vine)*: se ha usado por siglos en la medicina tradicional china. Se dice que puede tener efectos antiinflamatorios, pero también puede suprimir el sistema inmune. Una revisión sistemática mostró efectos adversos como irregularidades menstruales, osteoporosis, y en los hombres, infertilidad. También puede producir diarreas, malestar gástrico, cefaleas y alopecia.

Además hay estudios con **jengibre, té verde y cúrcuma** que todavía no son concluyentes y que, si bien pueden sugerir cierto efecto antiinflamatorio, este todavía no ha sido demostrado en humanos.

- También se estudian métodos de medicina **ayurvédica**, de la India, que aún son insuficientes;
- La **balneoterapia**, que se usa en algunos países del este de Europa, no tiene estudios confiables que permitan llegar a conclusiones concretas; y
- Algunas **dietas**, por ejemplo de tipo vegetariano, mediterráneas o ayunos periódicos no han tenido estudios de investigación concluyentes. Una desventaja de las dietas es que es muy difícil mantenerlas y algunas pueden llevar inclusive a cierta desnutrición o malnutrición.

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