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KEEP REMISSION IN THE COMFORT OF HOME...
...WHEREVER HOME MAY BE AT THE MOMENT

HUMIRA® (adalimumab) is the only FDA-approved self-injectable biologic used in both moderate to severe Crohn's Disease and Ulcerative Colitis

Indications[1]

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. The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to anti-TNF agents.

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.

Self-administration Considerations[1]

HUMIRA can be self-injected at home or almost anywhere with medical follow-up, after a physician determines that it is appropriate and after proper training in injection technique. Instruct patients to refer to storage instructions found in the Medication Guide.

HUMIRA®
adalimumab

Important Safety Information[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. 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.

- Do not start HUMIRA in patients with an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- Consider the risks and benefits of treatment in patients with chronic or recurrent infection or with underlying conditions which may predispose them to infection, patients who have been exposed to TB, patients with a history of opportunistic infection, or patients who have resided or traveled in regions where TB or mycoses are endemic.
- Patients who develop a new infection should undergo a prompt and complete diagnostic workup, and appropriate antimicrobial therapy should be initiated.
- Drug interactions with biologic products: Concurrent use of anakinra or abatacept with HUMIRA is not recommended, as the combination of anakinra or abatacept with TNF blockers has been associated with an increased risk of serious infections. This risk has also been observed with rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. 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. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has 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 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.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- More cases of malignancies were observed among HUMIRA-treated patients compared to control patients in clinical trials.
- Non-melanoma skin cancer (NMSC) has been reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use.
- Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration.
- If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

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. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after treatment with HUMIRA.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation.
- Exercise caution when considering resumption of HUMIRA therapy after appropriate treatment for HBV.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated in rare cases with new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia (e.g., thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA in patients with significant hematologic abnormalities.

CONGESTIVE HEART FAILURE

- Worsening or new onset congestive heart failure (CHF) may occur.
- Exercise caution in patients with CHF and monitor them carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome.
- Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (incidence >10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

Reference: 1. HUMIRA Injection [package insert].

Please see Brief Summary of full Prescribing Information on following pages.

HUMIRA®
adalimumab

abbvie

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HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNINGS: 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 has 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 or new tuberculosis infections have been observed in patients receiving HUMIRA, including patients who have previously received treatment for latent or active 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. 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 has 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.

Hypersensitivity Reactions

In postmarketing experience, anaphylaxis and angioneurotic edema have been reported rarely 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 overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

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

Hepato-biliary disorders: Liver failure

Immune system disorders: Sarcoidosis

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 to provide recommendations regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, and Ps.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with

CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

Nursing Mothers

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than juvenile idiopathic arthritis (JIA) have not been established.

Juvenile Idiopathic Arthritis

In the JIA trial, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age. HUMIRA has not been studied in children less than 4 years of age, and there are limited data on HUMIRA treatment in children with weight <15 kg.

The safety of HUMIRA in pediatric patients in the JIA trial was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Warnings and Precautions]*.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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GASTROENTEROLOGY & HEPATOLOGY

THE GASTRO & HEP REPORT

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- The 63rd Annual Meeting of the American Association for the Study of Liver Diseases

  November 9–13, 2012 • Boston, Massachusetts

- The 2012 Advances in Inflammatory Bowel Diseases

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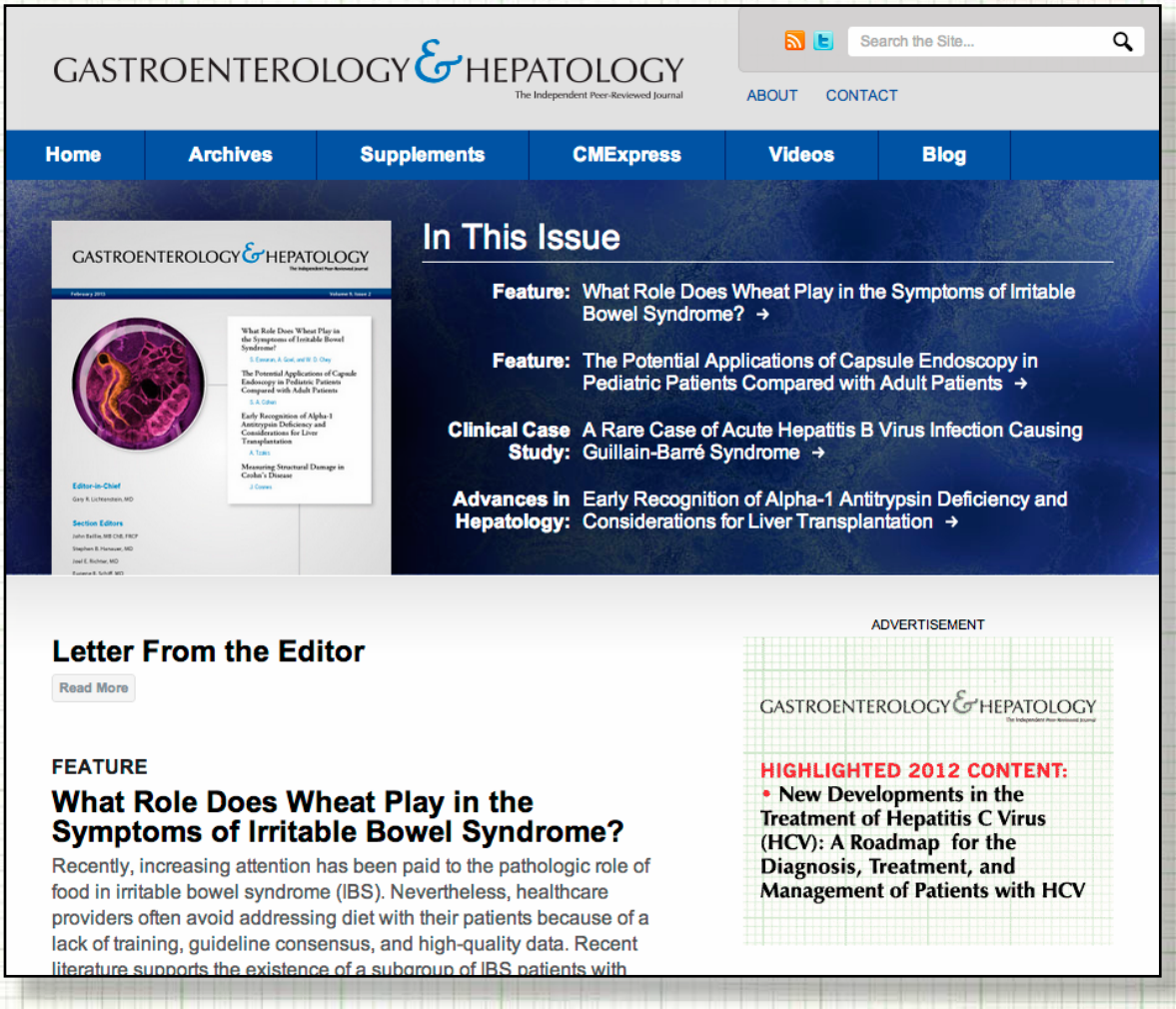

The new, redesigned web portal of *Gastroenterology & Hepatology*

Presentations in IBS

Mesalamine Granules Provide Relief of Symptoms in Patients with Irritable Bowel Syndrome with Diarrhea

Extended-release mesalamine granule capsules are currently indicated for the maintenance of remission in ulcerative colitis. Uncontrolled studies suggest that aminosalicylate therapy may be beneficial in patients with irritable bowel syndrome with diarrhea (IBS-D). Jeffrey Aron, from the California Pacific Medical Center in San Francisco, reported the results of a randomized, double-blind, placebo-controlled, multicenter phase II study at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #7). The study was designed to evaluate the efficacy of extended-release mesalamine granules for the treatment of IBS-D.

A total of 148 patients with IBS-D were randomly selected to receive either extended-release mesalamine granules at a dosage of 750 mg/day or 1,500 mg/day or else placebo for 12 weeks. Eligible patients had IBS-D as defined by Rome III criteria and had experienced diarrhea with no constipation in the 7–13 days before receiving the first dose of the study drug.

Patients described as weekly responders in relation to abdominal pain were defined as those patients who had a 30%-or-greater improvement from baseline in a weekly average abdominal pain score on a 10-point scale. Weekly responders in relation to stool consistency were defined as those patients who had a 50%-or-greater reduction in the number of days per week in which stool consistency was type 6 or 7 compared with baseline, according to the Bristol Stool Scale. Patients defined as being monthly responders were those who were weekly responders in relation to both abdominal pain and stool consistency for at least 2 of 4 weeks.

A significantly greater number of patients who were treated with 1,500 mg extended-release mesalamine granules were monthly responders compared with patients who were receiving placebo (47% vs 28%; P=.0432). Although more patients receiving 750 mg/day of extended-release mesalamine granules were monthly responders compared with those receiving placebo, the difference in the rate of response did not reach statistical significance (32% vs 28%; P=.6059).

The adverse event profiles were similar between the extended-release mesalamine granule dosage groups and the mesalamine therapy groups and the placebo group.

Linaclotide Acts Rapidly on Abdominal and Bowel Symptoms in Patients with Irritable Bowel Syndrome with Constipation

Linaclotide achieved rapid improvement in symptoms, compared with placebo, in patients with irritable bowel syndrome with constipation (IBS-C), according to Lin Chang, of the Division of Digestive Diseases at the University of California Los Angeles, who presented study results during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P1559). Chang and colleagues evaluated the changes in abdominal and bowel symptoms from baseline through the first 7 days of treatment with linaclotide.

Patients qualified for each study if they had IBS-C and met modified Rome II criteria. In 2 phase III trials, patients were randomly selected to receive either 290 mg/day linaclotide (n=805) or placebo (n=797). Pooled results of the intent-to-treat population showed that patients treated with linaclotide achieved a significant mean percent improvement in abdominal bloating (8% vs 4%; P<.05) and fullness (9% vs 4%; P<.05) on Day 1, pain (12% vs 7%; P<0.05) and discomfort (11% vs 7%; P<.05) by Day 2, and cramping (15% vs 10%; P<.05) by Day 3, compared with patients receiving placebo.

Stool consistency and straining on Day 1 also were significantly improved in the linaclotide group compared with the placebo group (P<.0001). More patients receiving linaclotide than those receiving placebo reported 1 or more spontaneous bowel movements on each of the first 7 treatment days (Day 1, 49% vs 24%; Day 2, 57% vs 40%; Day 3, 54.3% vs 42%; Day 4, 55% vs 40%; Day 5, 55% vs 39%; Day 6, 54% vs 39%; Day 7, 50% vs 39%; P<.0001). The same was also true for patients who reported a complete spontaneous bowel movement.

Although the median time to the first spontaneous bowel movement was the same—2 days—for patients in both treatment groups, the median time to the first complete spontaneous bowel movement was significantly shortened in the linaclotide group compared with the placebo group (5 vs 20 days; P<.0001). During Week 1, patients treated with linaclotide had an average of 6.6 spontaneous bowel movements and 2.4 complete spontaneous bowel movements. These frequencies of spontaneous bowel movements were significantly higher than those reported by patients receiving placebo (3.5 and 0.9, respectively; P<.0001). The incidence of diarrhea during the first week

of treatment was 10% among patients treated with linaclotide, which was higher than that reported in patients receiving placebo (0.4%).

Linaclotide May Increase Bowel Movements and Lessen Straining in Patients with Chronic Constipation

A post-hoc analysis of pooled data from 2 phase III trials showed that linaclotide therapy can increase bowel movements and lessen straining in patients with chronic constipation. The findings were delivered by Satish S. Rao, of the Georgia Health Sciences University Medical Center, during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #455).

The goals of this study were 2-fold: 1) to evaluate the effects of linaclotide compared with placebo on the distribution of bowel movements occurring with the use of rescue medications, spontaneous bowel movements, and complete spontaneous bowel movements, and 2) to determine the effects of linaclotide compared with rescue medication on straining associated with spontaneous bowel movements.

All patients had an average of fewer than 3 complete spontaneous bowel movements per week and 6 or fewer spontaneous bowel movements per week during a 2-week pretreatment period. In this study, spontaneous bowel movements were defined as those occurring in the absence of rescue medication, and complete spontaneous bowel movements were accompanied by a patient-reported feeling of complete evacuation.

A total of 1,271 patients were included in the pooled intent-to-treat population, including 423 patients who received placebo and 430 patients who received linaclotide at a dosage of 145 mg/day and 418 patients who received linaclotide at a dosage of 290 mg/day. The rates of spontaneous and complete spontaneous bowel movements were significantly increased with linaclotide therapy compared with placebo (38% for the 145 mg/day dosage and 42% for the 290 mg/day dosage vs 22% for placebo).

During the treatment period, more patients treated with linaclotide reported decreased straining compared with patients receiving placebo. The proportion of patients who reported a little straining or none at all was 69% for both linaclotide cohorts versus 49% for the cohort receiving placebo who used rescue medication.

Benefit Was Demonstrated for Lubiprostone in Patients with Irritable Bowel Syndrome with Constipation

Global response criteria for lubiprostone provided clinically meaningful measures of treatment benefit in relation to symptoms of irritable bowel syndrome with constipation (IBS-C) and were consistent with improvement in individual secondary symptoms, according to Raymond M. Panas and colleagues from Sucampo Pharma Americas, Inc. in Bethesda, Maryland, whose study results were presented during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P1009). The researchers conducted a sensitivity analysis that compared previously established global response criteria for evaluating treatments for IBS-C with improvement in individual symptoms.

Data from 1,421 patients were pooled from 2 randomized, double-blind, 12-week studies that compared lubiprostone (8 mg twice daily) with placebo for the treatment of IBS-C. The primary endpoint—based on patient response to the question "How would you rate your relief of IBS symptoms [abdominal discomfort/pain, bowel habits, and other IBS symptoms] over the past week compared with how you felt before you entered the study?"— was rated on a 7-point balanced scale. The monthly response was defined by patient-reported symptom rating as either significantly relieved for 2 weeks or more or moderately relieved for 4 weeks without having an increase from baseline in the use of rescue medication, a discontinuation due to lack of efficacy, or any ratings of moderate or significant worsening. Individual secondary symptoms, which included abdominal discomfort/pain, abdominal bloating, and constipation severity, were rated on a 5-point scale, on which a 1-point shift was considered to be clinically meaningful.

Global response was significantly improved with lubiprostone treatment versus placebo ($P<.0005$). Global response appeared to be closely related to improvement in individual symptoms. Responding patients achieved a 1-point-or-greater increase in the mean change from baseline for each symptom. Patients who failed to respond to treatment showed little change (<1 point). The global response criteria demonstrated a high sensitivity for detecting treatment-dependent changes of individual IBS-C symptoms (0.923 for abdominal discomfort/pain; 0.936 for abdominal bloating; and 0.935 for constipation severity).

A Tri-Component Endpoint in Irritable Bowel Syndrome Shows Value in Response Assessment

A tri-component endpoint for symptoms of irritable bowel syndrome (IBS) without constipation is responsive and correlates with all daily symptoms of IBS with diarrhea (IBS-D), according to Anthony J. Lembo, of the Beth Israel Deaconess Medical Center in Boston, Massachusetts, who presented findings on the use of a tri-component endpoint for assessing

response to treatment in patients with IBS-D during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P1571A). Lembo and colleagues noted that current guidance from the US Food and Drug Administration recommends the use of a composite endpoint of 2 primary IBS-D symptoms: abdominal pain and stool consistency; however, this endpoint may ignore other gastrointestinal symptoms that patients consider to be important, such as urgency and bloating. Thus, the research team developed a tri-component endpoint that included a daily assessment of abdominal pain and stool consistency as well as global IBS symptoms.

Patient data were pooled from 2 phase III trials, TARGET 1 and TARGET 2. A total of 1,260 patients with IBS without constipation were randomly selected to receive either rifaximin (550 mg 3 times daily) or placebo for 2 weeks and then were evaluated for 10 weeks. IBS symptom severity for both global IBS symptoms and IBS-related abdominal pain was rated on a 7-point scale. Stool consistency was rated on a 5-point scale. The tri-component endpoint defined weekly responders as those patients who reported a 30%-or-greater improvement from baseline in abdominal pain, a 50%-or-greater improvement in the number of days in a week that they passed loose or watery stools, and a 1-point-or-greater improvement in the weekly average score of daily global IBS symptoms.

In both studies, as well as in pooled analysis, significantly increased improvements in all daily IBS symptom severity measures were observed at each study week in those responders defined by the tri-component endpoint compared with nonresponders. Results also suggested that the tri-component endpoint had convergent validity; it consistently correlated with all daily IBS symptom severity measures at each treatment week (Spearman correlation of ≥0.40 with other daily symptom severity measures).

Presentations in IBD

Results of GEMINI I: Vedolizumab Is Effective in Maintaining Clinical Remission in Patients with Ulcerative Colitis

Vedolizumab maintenance therapy showed efficacy in achieving clinical corticosteroid-free remission, with durable response, in patients with ulcerative colitis. These findings from GEMINI I, a phase III trial evaluating the efficacy and safety of the investigational anti-α4β7 integrin gut-selective monoclonal antibody vedolizumab, were reported by Brian G. Feagan, of the Robarts Research Institute in London, Ontario, Canada, at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #5).

A total of 895 adults with moderate to severely active ulcerative colitis who had failed at least 1 prior therapy received 2 induction doses of vedolizumab at Weeks 0 and 2. Patients with a clinical response at Week 6 (n=373) were then randomly selected to receive 46 weeks of maintenance therapy with vedolizumab, administered intravenously at a dosage of 300 mg every 4 or 8 weeks, or placebo. The primary outcome was clinical remission at Week 52.

Superior outcomes were achieved in significantly more patients treated with vedolizumab than placebo. The rate of clinical remission was 45% for patients receiving vedolizumab every 4 weeks, 42% for patients receiving vedolizumab every 8 weeks, and 16% for patients receiving placebo (P<.0001). The rate of steroid-free remission was 45% for the 4-week vedolizumab arm, 31% for the 8-week vedolizumab arm, and 14% for the placebo arm (P<.0001 and P=.0120 for the 4-week and 8-week vedolizumab arms, respectively). The rate of mucosal healing also was significantly improved with both 4-week (56%) and 8-week (52%) vedolizumab compared with placebo (20%; P<.0001). Clinical remission and durable clinical response were achieved regardless of prior exposure to tumor necrosis factor alpha (TNF-α) inhibitors.

The rates of clinical remission among patients with prior TNF-α inhibitor failure were 35% for vedolizumab every 4 weeks, 37% for vedolizumab every 8 weeks, and 5% for placebo. The comparable rates among patients with no prior TNF-α inhibitor exposure were 48%, 46%, and 19%, respectively.

There was no significant increase in the frequency of adverse events, including the rates of opportunistic or enteric infections, among patients treated with vedolizumab compared with patients receiving placebo.

GEMINI II Results: Vedolizumab Shows Good Response in Treatment-Resistant Crohn's Disease

Vedolizumab maintenance therapy was associated with higher rates of remission and an enhanced corticosteroid-free response compared with placebo in patients with Crohn's disease (CD) that was resistant to immunsuppressive agents and tumor necrosis factor alpha (TNF-α) inhibitors. These findings from the GEMINI II trial were presented by Stephen Hanauer of the University of Chicago Medical Center at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #42).

The trial enrolled 1,115 patients with moderate-to-severe CD. A total of 461 patients who had received induction therapy, consisting of 2 intravenous 300-mg doses of vedolizumab, showed a response at Week 6 and went on to be randomly selected to receive vedolizumab maintenance therapy (300 mg intravenously) every 4 or 8 weeks or else placebo.

Significantly superior rates of clinical remission (36% for the 4-week arm and 39% for the 8-week arm) were achieved with vedolizumab compared with placebo (22%; P=.0042 and P=.0007 for the 4- and 8-week vedolizumab arms, respectively). Significantly superior rates of corticosteroid-free remission were achieved as well in patients receiving active treatment (29% in the 4-week and 32% in the 8-week vedolizumab arm vs 16% in the placebo arm; P=.0450 and P=.0154 for the 4- and 8-week vedolizumab arms, respectively). Further, the rate of remission was improved with vedolizumab regardless of whether patients had histories of failing TNF-α inhibitor therapy or had no prior exposure to TNF-α inhibitors.

The rate of enhanced clinical response, defined as a decrease in the CD Activity Index of 100 points, was also significantly improved in both vedolizumab arms compared with the placebo arm (P=.0132 and P=.0053 for the 4- and 8-week vedolizumab arms, respectively). The rate of durable remission also was improved with vedolizumab therapy; however, the difference compared with placebo did not reach statistical significance.

The exposure-adjusted rates of all adverse events, including serious infections, were comparable across the 3 treatment groups. However, the exposure-adjusted rate of serious adverse events was increased in the placebo arm versus either vedolizumab arm.

Antibody Production May Be Linked to Lack of Response to Adalimumab Therapy

Up to a third of patients with Crohn's disease (CD) will show a primary nonresponse to tumor necrosis factor alpha (TNF-α) inhibitor therapy, and an additional 30–40% of patients will lose response to initial TNF-α therapy during the first year of treatment. Dose escalation or a switch to another anti–TNF-α therapy is often required to maintain a response in patients in whom secondary resistance develops. Failure of anti–TNF-α therapy may, in part, be attributed to low serum drug levels and/or the development of antidrug antibodies. Monitoring of both of these parameters is emerging as an important strategy in the management of inflammatory bowel disease (IBD).

To analyze adalimumab levels in relation to production of antibodies to adalimumab, Shui Long Wang, from Prometheus Laboratories, Inc. in San Diego, California, and colleagues used the homogeneous mobility shift assay (HMSA) to measure adalimumab levels and antibodies to adalimumab in serum samples of 100 patients with IBD who had initially responded to adalimumab therapy for at least 3 months but were beginning to lose response to treatment. Findings were reported during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P1499).

The HMSA demonstrated a lower limit of detection of 0.026 mg/mL for antibodies to adalimumab and 0.018 mg/mL for adalimumab. The coefficient of variation was less than 15%, and the accuracy was within 20% of detection for both assays. Tolerance for adalimumab in antibodies to adalimumab HMSA reached 40 µg/mL. Using serum samples from 100 drug-naïve healthy individuals, a cutoff threshold value of 0.55 U/mL was determined for antibodies to adalimumab and 0.66 µg/mL was calculated for serum adalimumab levels. Overall, antibodies to adalimumab were present in 40% of samples.

Approximately one third (36%) of the patients who were losing response to adalimumab had a serum adalimumab level of less than 3 mg/mL. Of these, 58% were positive for antibodies to adalimumab. However, antibodies to adalimumab were present in only 4 (18%) of 22 patients whose serum adalimumab level increased to greater than 20 mg/mL.

Adalimumab Shows Promise for Treatment of Moderately to Severely Active Ulcerative Colitis

Efficacy results suggest that adalimumab may hold promise in the treatment of severe ulcerative colitis (UC), according to Jean-Frederic Colombel, of the Centre Hospitalier Universitaire de Lille, France, who discussed interim results of the ongoing adalimumab UC development program extension study at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P387). The development program consists of the ULTRA 1 and ULTRA 2 clinical trials followed by an ongoing multicenter open-label extension study.

ULTRA 1 and ULTRA 2 both demonstrated that adalimumab effectively induced remission in patients with moderately to severely active UC. Patients enrolled in the extension study who were already receiving open-label adalimumab weekly continued with the same regimen. Patients who entered the extension study from a blinded cohort or who were receiving open-label adalimumab at a dosage of 40 mg every other week received adalimumab at this dosage during the extension study. In cases of disease flare or nonresponse, patients who entered the extension study from a blinded cohort were permitted to increase their adalimumab dosage to 40 mg weekly at Week 12 or thereafter. The same protocol was allowed for patients from open-label cohorts who were in clinical response when they entered the extension study. Those who had a flare or no response were permitted to increase their dosage at Week 2. The partial Mayo score, defined as the Mayo score without the endoscopy subscore, was determined at each study visit.

On the day of the first adalimumab dose in the extension study, the observed mean partial Mayo score was 5.9. This score decreased gradually over the extension study, reaching a mean of 4.2 at 4 weeks, 3.9 at 8 weeks, 2.6 at 52 weeks, and 1.8 at 112 weeks of treatment. Of the 588 patients enrolled in the extension study, 351 (60%) achieved clinical remission by Week 60. No new adverse events have been reported.

New Therapy Shows Little Impact on Colorectal Cancer Risk in Patients with Ulcerative Colitis

No significant difference in colorectal cancer risk was seen between patients receiving adalimumab and standard therapy for treatment of ulcerative colitis (UC), reported Jean-Frederic Colombel, from the Centre Hospitalier Universitaire de Lille, France, at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P389). To assess whether adalimumab showed a benefit over standard therapy in relation to colorectal cancer risk in patients with UC, Colombel and colleagues identified 23,867 patients, age 18–64 years, from a patient database for years 2000–2010. Patients who had initiated adalimumab therapy for UC during this time were assigned to the adalimumab group (n=581), while patients who had initiated corticosteroid, aminosalicylate, or immunosuppressant therapy (without concomitant

adalimumab, etanercept, or infliximab) were assigned to the standard therapy group (n=23,286).

For the 6 months prior to baseline, patients could have no evidence of colorectal cancer; benign neoplasm of the colon, rectum, or anal canal; or any other malignancies. The time to colorectal cancer diagnosis was calculated using Kaplan-Meier survival curves and Cox proportional-hazard models.

The risk of colorectal cancer at 1 and 2 years after initiating therapy was similar between the adalimumab- and standard-therapy groups before adjusting for baseline demographics (age, sex, and year of treatment initiation) and comorbidity factors (noninfective gastroenteritis, colitis, and gastrointestinal hemorrhage). At 1 year, the colorectal cancer–free rate was 100% in both groups. The comparable 2-year colorectal cancer–free rates were the same; however, after adjusting for baseline factors, colorectal cancer was approximately 1.36-fold less likely to develop in patients treated with adalimumab by Year 2 compared with patients receiving standard therapy. Statistical significance was not reached (hazard ratio, 0.735; 95% confidence interval, 0.101–5.373; *P*=.762).

Adalimumab Therapy Is Associated with Reduced Hospitalization and Colectomy Rates in Patients with Ulcerative Colitis

Rates of hospitalizations and colectomies in patients with ulcerative colitis (UC) who had a first response to adalimumab therapy were reduced compared with rates in patients receiving placebo, reported Brian G. Feagan, of the Robarts Research Institute in London, Ontario, Canada, during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P424). Feagan and colleagues studied the effect of a 160/80/40-mg adalimumab regimen on reduction of risk in all-cause and UC-related hospitalization and colectomy, specifically among patients with an initial response to adalimumab (n=939). The investigators used data from the ULTRA 1 and ULTRA 2 trials, both of which demonstrated significant reductions in hospitalization rates and nonsignificant reductions in colectomy rates in patients receiving adalimumab for treatment of moderately to severely active UC.

Two gastroenterologists blinded to the treatment arms reviewed hospitalization and colectomy rates based on the safety reports of the patients in the study cohort. Hospitalizations of patients treated with adalimumab who had an initial nonresponse through Week 8 were counted but were censored after Week 8 to reflect the clinical practice pattern of continuing treatment in initial adalimumab responders.

Compared with the placebo group, a 35% reduction in the number of patients hospitalized for any reason and a 36% reduction in the number of hospitalizations for any reason were seen in the adalimumab group. For the number of patients who had an all-cause hospitalization, the person-year–based incidence rate was 17% for adalimumab versus 26% for placebo (*P*=.035). The person-year–based incidence rate for the number of hospitalizations was 20% for adalimumab versus 31% for placebo (*P*=.015). Both the rate and number of UC-related hospitalizations also were significantly reduced (55% and 56%, respectively). The person-year–based incidence rate for the number of patients who underwent a UC-related hospitalization was 10% for adalimumab versus 22% for placebo (*P*=.001), and the person-year–based incidence rate for the number of UC-related hospitalizations was 11% versus 25% (*P*<0.001). The difference in the person-year–based incidence rate for colectomy did not reach statistical significance between the adalimumab and placebo groups (2% vs 4%; *P*=.099).

Presentations in GERD

Prevalence and Distinguishing Features of PPI-Responsive Esophageal Eosinophilia and Eosinophilic Esophagitis Are Defined

The prevalence and distinguishing characteristics of proton pump inhibitor–responsive esophageal eosinophilia (PPI-REE) and eosinophilic esophagitis (EoE) were defined in a prospective study that aimed to determine the prevalence of PPI-REE and EoE in patients undergoing esophagogastroduodenoscopy (EGD). The study was presented by Evan S. Dellon, from the Division of Gastroenterology at the University of North Carolina Chapel Hill, at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #48).

Between 2009 and 2011, 173 patients with dysphagia revealed by EGD were enrolled in the study conducted by Dellon and colleagues. Esophageal biopsies were used to determine the maximum eosinophil count per high-power field (hpf). Patients with 15 or more eosinophils/hpf were treated twice daily with a PPI for 8 weeks, after which the EGD was repeated. Patients who exhibited persistent symptoms and 15 or more eosinophils/hpf received a diagnosis of EoE, but PPI-REE was diagnosed in cases of symptomatic and histologic response, defined as the finding of fewer than 15 eosinophils/hpf.

Of the 173 patients enrolled, 66 (38%) had an eosinophil count of 15 or more eosinophils/hpf. Following PPI treatment, a diagnosis of EoE was made in 40 (23%) patients, and 24 (14%) patients had a diagnosis of PPI-REE. EoE or eosinophilic gastroenteritis was diagnosed in 1 (2%) patient.

Among the 24 patients with PPI-REE, 9 (38%) had clinical features consistent with gastroesophageal reflux disease (eg, heartburn and hiatal hernia), whereas 12 (50%) had clinical features consistent with EoE, including dysphagia and food impaction. Three (12%) patients with PPI-REE had indeterminate clinical features. Compared with patients with EoE, those with PPI-REE were more likely (P<.05) to be older (age, 36 years vs 48 years), male (63% vs 88%), and have erosive esophagitis (5% vs 21%) or a Schatzki ring (2% vs 21%). Patients with PPI-REE were less likely (P<.05) to have esophageal rings (90% vs 63%), diffuse narrowing (42% vs 8%), linear furrows (88% vs 58%), or decreased vascularity (32% vs 0%). There was no difference in the maximum eosinophil count between patients with a diagnosis of PPI-REE and those with a diagosis of EoE (50 vs 64 eosinophils/hpf).

Patients with Type 2 Diabetes May Be at Increased Risk for Barrett Esophagus

Although a strong association exists between central obesity and an increased risk of Barrett esophagus and esophageal adenocarcinoma, the reason remains unclear. Findings suggesting a potential epidemiologic link between type 2 diabetes and Barrett esophagus were reported by Prasad G. Iyer of the Mayo Clinic College of Medicine in Rochester, Minnesota, at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #49). This was a population-based case-control study using patient data from the General Practice Research Database of the United Kingdom.

Cases of Barrett esophagus (n=14,245) were compared with controls (n=70,361), matched for age, sex, enrollment date, duration of follow-up, and practice region. The association of an initial diagnosis of type 2 diabetes prior to a diagnosis of Barrett esophagus was calculated after adjusting for known risk factors for Barrett esophagus, including cigarette smoking, alcohol consumption, body mass index, and gastroesophageal reflux disease.

Baseline characteristics showed that cases and controls were comparable for age and sex, but cases were more likely than controls to have ever smoked cigarettes or consumed alcohol. The prevalence of type 2 diabetes before a diagnosis of Barrett esophagus was higher in cases versus controls (6% vs 5%; P<.001). The same was also true for the mean body mass index (27.0 kg/m^2 vs 26.8 kg/m^2; P<.001).

A diagnosis of type 2 diabetes was associated with a 2-fold increased risk of Barrett esophagus, independent of other risk factors. This association was stronger in men (odds ratio [OR], 2.03; 95% confidence interval [CI], 1.01–4.04) compared with women (OR, 1.37; 95% CI, 0.63–2.97). Having a diagnosis of type 2 diabetes for more than 1 year was also associated with a higher risk of Barrett esophagus (OR, 7.7; P=.004). Being overweight or obese prior to the diagnosis of Barrett esophagus was significantly associated with the disease (P=.013 and P=.08, respectively).

Failure of Empiric PPI Therapy May Rule Out a Suspected GERD Diagnosis

Most patients referred for testing to confirm a suspected diagnosis of gastroesophageal reflux disease (GERD) after failing empiric proton pump inhibitor (PPI) therapy had normal 24-hour pH/impedance study results while off acid

suppressive therapy, reported Fong-Kuei Cheng of the Walter Reed National Military Medical Center in Bethesda, Maryland, during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P3). The study investigated whether a final diagnosis of GERD was made in patients referred for a 24-hour esophageal pH test and impedance testing.

A total of 348 patients who had undergone 24-hour esophageal pH and impedance testing while off of acid suppressive therapy between years 2006 and 2011 were identified from a clinical database. The mean age of the patient set was 47±13 years, and just over half (55%) were men. The majority of patients had received empiric PPI treatment before testing, and, of these, most (68%) were assigned to a daily pharmacotherapy regimen. Most patients (72%) had a normal Johnson-DeMeester score on 24-hour esophageal pH testing.

Among the 97 (28%) patients with abnormal scores (≥22), 56 (58%) had typical GERD symptoms, including heartburn or acid regurgitation, and 41 (42%) had atypical symptoms, including chest pain, chronic cough, hoarseness, dysphagia, or dyspepsia (P=.023). Although there were no significant differences in relation to race or age of the patients with abnormal 24-hour esophageal pH testing, a significantly greater proportion of men were found to have an abnormal Johnson-DeMeester score compared with women (34% vs 20%; P=.004).

Seventy-five (22%) patients had abnormal findings on impedance testing. The majority of patients (87%) who had normal 24-hour esophageal pH tests also had a normal impedance tests. However, fewer than half (44%) of the patients with an abnormal 24-hour esophageal pH test had a normal impedance test (kappa=.331; P<.001).

Esophageal Body Hypomotility and Acid Exposure Are Independent Predictors of Barrett Esophagus

The associations between Barrett esophagus and esophageal dysmotility and reflux were described by Wai-Kit Lo of the Brigham and Women's Hospital at Harvard Medical School in Boston, Massachusetts, during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P5). Lo and colleagues used new technologies, such as high-resolution manometry and combined multichannel intraluminal impedance and pH, to assess esophageal motor characteristics and reflux profiles, such as acid and bolus exposure time. All patients included in the study had undergone esophagogastroduodenoscopy (EGD) within 2 years of the esophageal physiologic testing and had a diagnosis of Barrett esophagus based on EGD and histopathologic findings.

A total of 23 cases of Barrett esophagus and 69 controls (matched by age at endoscopy, gender, and race) who had been treated over a 5-year period at a tertiary care center were identified. Patients with a history of gastroesophageal surgery were excluded from the study.

A univariate analysis showed that a history of cigarette smoking, esophageal body hypomotility (defined as the average of esophageal body contraction amplitudes <30 mmHg or >30% failed sequences), and increased acid exposure time were significantly associated with Barrett esophagus. In a multivariate analysis that was adjusted for smoking history, each of these factors remained significant independent predictors of Barrett esophagus: increased acid exposure time (odds ratio [OR], 6.22; P=.008), esophageal body hypomotility (OR, 7.78; P=.01), and history of cigarette smoking (OR, 4.82; P=.04).

PPIs and Laparoscopic Antireflux Surgery Are Comparable in Long-Term Symptom Control of GERD

Proton pump inhibitors (PPIs) and laparoscopic antireflux surgery (LARS) were shown to have similar efficacy in long-term symptom control of gastroesophageal reflux disease (GERD) in a study by Jyothsna Talluri and colleagues from the McLaren Regional Medical Center in Flint, Michigan. The team presented study results of an evidence-based review during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P8).

Two randomized trials published between 1980 and 2011 that met the inclusion criteria for the review, including a minimum follow-up of 3 years, were identified. The primary outcome in the first study was a 5-year remission rate, which was significantly higher among patients treated with the PPI esomeprazole than LARS (92% vs 85%; P=.05). However, this comparison lost significance following best-case scenario modeling of the effects of study dropout.

The 5-year prevalence of some symptoms was different—and, in some cases, significantly different—in the esomeprazole group compared with the LARS group. Symptoms included heartburn (16% vs 8%; P=.14), acid regurgitation (13% vs 2%; P<.001), dysphagia (5% vs 11%; P<.001), bloating (28% vs 40%; P<.001), and flatulence (40% vs 57%; P<.001).

In the second study, the efficacy of PPI therapy and LARS at 3 years was compared using the GERD symptom scale (GERSS), which was the primary treatment outcome in this trial. At 3 years, GERSS scores were statistically similar between the groups receiving PPI therapy and LARS (9.05 vs 6.21; P=.17). However, LARS was associated with a greater frequency of heartburn-free days

compared with PPI therapy (6.81 vs 5.98; *P*=.007). Acid reflux symptoms, measured by 24-hour esophageal pH testing, improved from a GERSS score of 9.46 at baseline to a score of 4.29 at 3 years in patients receiving PPI therapy. Acid reflux symptoms improved from a GERSS score of 10.26 at baseline to a score of 2.11 at 3 years in patients who underwent LARS. The change from baseline to 3 years did not statistically differ between the PPI and LARS groups (*P*=.13).

Electrical Stimulation Therapy of the Lower Esophageal Sphincter May Be Useful in Treatment-Refractory GERD

Preliminary results of an international multicenter trial evaluating the efficacy and safety of lower esophageal sphincter electrical stimulation therapy (LES-EST) in patients with refractory gastroesophageal reflux disease (GERD) show promise and were presented by Albert J. Bredenoord of the Academic Medical Center in Amsterdam, The Netherlands, during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P581).

Patients with GERD who were partially responsive to PPI therapy were included if they had the following characteristics: an off–proton pump inhibitor (PPI) GERD health-related quality-of-life score of more than 20, an improvement in score of more than 5 points while on PPI therapy, a LES end-expiratory pressure of greater than 5 mmHg, a 24-hour esophageal pH of less than 4 for more than 5% of the time interval, and a hiatal hernia. At the time of presentation, 11 patients had been enrolled and had undergone implantation. The mean age of the patients was 54 years, and more than half (n=7) were men.

During the implantation procedure, a small bowel trocar perforation, which was successfully repaired, occurred in 1 patient. LES-EST is continuing in the remaining 10 patients. Of these 10, 6 (60%) have completed a 3-month evaluation and 3 (30%) have completed a 6-month evaluation.

The median off-PPI GERD health-related quality-of-life score at baseline was 32 (interquartile range: 25–38), which was found to be improved to 9 at the 3-month evaluation following LES-EST (*P*<.001). This improvement remained stable at the 6-month evaluation (*P*=.05). The median esophageal acid exposure at baseline was 12% (interquartile range: 8.8–15), which improved to 8% (interquartile range: 2.4–12) at the 3-month evaluation and 7% (interquartile range: 0.2–15.3) at the 6-month evaluation. Ten (91%) of the 11 patients enrolled were able to discontinue PPI therapy.

A total of 13 adverse events, including 1 serious adverse event, were reported in 4 patients. Of these, 9 (69%) events were related to the device or the procedure, 7 (54%) events were pain at the implant site, and 1 event was postoperative nausea.

Transoral Incisionless Endoscopic Fundoplication May Be an Option in Select Patients with Chronic GERD

Transoral incisionless fundoplication (TIF) may be a safe and effective therapeutic option in carefully selected patients with chronic gastroesophageal reflux disease (GERD) who have unsatisfactory outcomes with medical management or who choose to discontinue proton pump inhibitor (PPI) therapy, reported Peter G. Mavrelis of Internal Medicine Associates in Merrillville, Indiana, during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P1049). The presentation related results of a 12-month follow-up study of patients with chronic GERD who underwent treatment with TIF performed with an EsophyX device. The study included 100 consecutive patients with GERD who had failed medical management and/or had extraesophageal manifestations of GERD. The mean patient age at baseline was 52 years, the mean body mass index was 26.5 kg/m^2, and approximately one third (35%) of the study population were men. The average duration of GERD was 10 years, and the average duration of PPI use was 8 years.

No complications were reported either during or after the procedure. The procedure failed in 6 patients who underwent revision either with laparoscopic Nissen fundoplication (n=5) or TIF (n=1). Whereas 92 (92%) patients were on daily PPI therapy before the TIF procedure, 75 (75%) were able to discontinue PPI therapy after the TIF procedure (*P*<.001).

Slightly more than half (53%) of patients with an available 12-month pH test demonstrated either a normalization or a 50%-or-greater improvement in esophageal acid exposure. A significant improvement was observed in the mean GERD health-related quality-of-life score from when patients were receiving PPI therapy to after the TIF procedure (23.4 vs 6.6; *P*<.001). A significant reduction in the average heartburn score (16.1 vs 4.3; *P*<.001) and regurgitation score (13.6 vs 3.2; *P*<.001) were also seen.

Most patients experienced an elimination of daily bothersome heartburn (65%) and regurgitation (86%). Atypical symptoms also were improved, demonstrated by a reduction in the mean Reflux Symptom Index score from 19.9 to 7.9 (*P*<.001).

At baseline, 80% of patients were dissatisfied with their current health condition; this dissatifaccction rate decreased to 15% after TIF. De novo dysphagia was reported in 2 patients and bloating in 1 patient.

Presentations in Endoscopy

Peroral Endoscopic Myotomy Demonstrates Efficacy and Safety

Peroral endoscopic myotomy (POEM) improves on natural orifice transluminal endoscopic surgery (NOTES), allowing for the treatment of achalasia. Stavros Stavropoulos and colleagues from the Winthrop University Hospital in Mineola, New York, presented their experience with POEM at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #6). Their findings reflect the first time that POEM has been performed outside of Japan and the first time worldwide that POEM has been performed by a gastroenterologist.

A total of 31 patients with achalasia (mean age, 51.8 years) underwent POEM with NOTES between years 2009 and 2012 and were included in the study. Presurgical evaluation included an office visit, upper endoscopy, barium swallow, computed tomography imaging of the chest and abdomen, and esophageal manometry. The primary outcome of this analysis was symptom resolution, defined as a decrease in the Eckardt score to 3 or less. Secondary outcomes included adverse events, postprocedure lower esophageal sphincter (LES) pressure, length of stay, and reflux symptoms or use of antacids. The investigators noted that their technique differed from the technique published in the literature and used in Japan. For example, although balloon inflation was initially used for tunnel dissection, the technique used by Stavropoulos and colleagues involved a knife that allows simultaneous submucosal injection and dissection and is a method that may be more accessible to Western gastroenterologists who do not have extensive experience with endoscopic submucosal dissection.

Patients were observed overnight following the procedure and underwent a barium swallow at 24 hours postsurgery to assess for presence of a leak. A clear liquid diet was initiated if the barium swallow results were negative, and the patient was discharged with a 7-day antibiotic therapy regimen. The liquid diet was switched to a soft diet at 1 week postsurgery.

The success rate of POEM was 94%. Treatment failed in 2 patients who had recurrent symptoms at 3 months (both responded to pneumatic dilation). Significant reductions were observed in both Eckardt score (7.5 to 1.1; $P<.0001$) and LES pressure (49mmHg to 19 mmHg; $P<.0001$). No complications were reported, including the need for intensive care unit stay, the need for hospital stays over 5 days, or the need for surgical interventions or blood transfusions. No patients underwent a surgical conversion or POEM-related readmission, and most (87%) patients did not require any post-POEM analgesia.

Rectal NSAIDs Are More Effective Than Pancreatic Stents in Preventing Post-ERCP Pancreatitis

Pancreatic stent placement and rectal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) have shown benefit in the prevention of postendoscopic retrograde cholangiopancreatography pancreatitis (PEP) in high-risk patients. However, a gap exists in the literature regarding randomized controlled trials that directly compare pancreatic stent placement with rectal NSAIDs in this setting. In comparing these procedures, Venkata S. Akshintala and colleagues from the Johns Hopkins Hospital in Baltimore, Maryland, deduced that rectal NSAIDs are more effective than pancreatic stents in preventing PEP in at-risk patients. This study, reported at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #55), was a systematic review and network meta-analysis aimed to compare rectal NSAIDs with PEP.

MEDLINE, EMBASE, and Cochrane Library databases were searched for randomized controlled trials meeting the inclusion criterion, which was being a full-text publication that reported the incidence of PEP as the primary outcome in high-risk patients receiving either rectal NSAIDs or pancreatic stenting. The investigators identified a total of 7 randomized controlled trials (n=1,168) that met the inclusion criterion. Of these, 5 trials evaluated pancreatic stenting, 1 trial evaluated rectal NSAIDs, and 1 trial evaluated both procedures. All 7 trials were simultaneously analyzed with the mixed treatment comparisons method of network meta-analysis, using a Bayesian approach. Treatments were evaluated according to the relative predictive probability of being ranked as the most effective.

The network meta-analysis showed that rectal NSAID use was more effective for prevention of PEP than either pancreatic stenting or placebo (probability of 0.66 for ranking as the best procedure). Pancreatic stenting ranked as the second best (probability of 0.33). Rectal NSAIDs were predicted to decrease the risk of PEP by 47% compared with pancreatic stenting and were associated with a relative risk reduction of 61.7% compared with pancreatic stenting for the prevention of PEP.

Covered or Uncovered Metal Stents: Utility Is the Same in the Management of Malignant Biliary Strictures

There were no differences in utility between covered and uncovered self-expanding metal stents for management of malignant biliary obstruction, according to Jeffrey H.

Lee from the MD Anderson Cancer Center in Houston, Texas. Lee reported study results during a poster session at the 2012 Annual Scientifc Meeting of the American College of Gastroenterology (Abstract #P650). Study outcomes included measurement of stent patency rate, overall survival, and complications in this retrospective cohort study from a single tertiary cancer center.

The study included 749 patients seen between years 2000 and 2011 who met the following inclusion criteria: 1) presence of a malignant biliary obstruction and presentation for endoscopic retrograde cholangiopancreatography, biliary decompression, and first-time metal stent placement; and 2) a history of malignant biliary obstruction, prior placement of a plastic biliary stent, and presentation for first-time metal stent placement. Of these patients, 171 received a covered self-expanding metal stent and 578 received an uncovered self-expanding metal stent. No difference was observed in median overall survival between the covered and uncovered groups (10.4 months vs 11.7 months; *P*=.84). The median time to recurrent biliary obstruction was 6.2 months for the group with a covered stent and 4.05 months for the group with an uncovered stent (hazard ratio, 1.06; 95% confidence interval, 0.70–1.58).

The proportion of patients who had recurrent biliary obstruction did not differ significantly between groups (*P*=.61), but the type of obstruction differed significantly. Tumor ingrowth occurred in 76% of patients with an uncovered stent and 9% of patients with a covered stent (*P*<.001). Patients with covered stents were more likely than those with uncovered stents to have tumor overgrowth (15% vs 2%), sludge stone (18% vs 3%), food debris (12% vs 5%), and stent migration (36% vs 2%). Acute pancreatitis also was more likely to occur in patients with covered stents than in patients with uncovered stents (6% vs 1%; *P*<.001). A total of 109 patients underwent surgery with the self-expanding metal stents in place. No stent-related intraoperative or postoperative complications were reported.

A Novel Teaching Tool Aids Trainees in Gastroenterology in Histologic Characterization of Diminutive Colorectal Polyps

Significant improvement in both accuracy of histologic characterization of polyps and the proportion of high-confidence diagnoses among trainees in gastroenterology was achieved via a novel computer-based teaching tool combined with short narrow-band imaging (NBI). The study, which was presented by Swati G. Patel from the University of Colorado at Denver School of Medicine during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P1096), aimed to determine the performance characteristics and learning curve among gastroenterology trainees who were taught characterization of diminutive polyp histology using NBI. A computer-based training tool and real-time NBI video clips were used in training to simulate clinical practice. The teaching module included previously validated NBI criteria that could be used to differentiate adenomas from hyperplastic polyps.

A total of 80 randomly distributed short videos of polyps (both adenomas and hyperplastic polyps) under NBI with magnification were viewed, after which participants reported the predicted polyp histology and their degree of confidence. Following each video assessment, feedback was provided regarding the histology, incorporating NBI criteria that supported the diagnosis. A total of 12 gastroenterology trainees were included in the study. Three trainees were in their first year of training, 4 were in their second year, and 5 were in their third year. They had a wide range of colonoscopy experience (from 51 to >500 colonoscopies performed).

There was a significant improvement in accuracy rates and the proportion of high-confidence predictions with increasing views of video blocks (*P*<.001 for the trend). The overall accuracy rate was 90%, with the accuracy rate steadily increasing with the numbers of videos viewed (83%, 86%, 93%, and 96% for the 1–20, 21–40, 41–60, and 61–80 video blocks, respectively). The overall positive predictive value was 95%, and the overall negative predictive value was 82%. A high degree of confidence had a greater positive correlation with a high accuracy rate than a low degree of confidence (96% vs 72%; *P*<.001). A substantial overall interobserver agreement was seen (kappa=.71), and no significant differences were observed in relation to year of training or extent of colonoscopy experience.

Endoscopic Ultrasound-Guided Rendezvous May Facilitate Pancreatic Endotherapy after Pancreaticoduodenectomy

Endoscopic ultrasound (EUS)-guided rendezvous following pancreaticoduodenectomy (PD) or pylorus-preserving PD (PPPD) can facilitate pancreatic endotherapy in select cases, according to Ihab I. El Hajj and colleagues from the Indiana University in Indianapolis, whose finding were presented during a poster session at the 2012 Annual Scientific Meeting of the American College of Gastroenterology (Abstract #P1212). Their study sought to characterize the performance characteristics of EUS rendezvous following classic PD or PPPD.

This was a single-center case series of EUS-guided rendezvous procedures that were performed following PD or PPPD between years 2005 and 2012. In all cases, the technique involved an EUS transgastric puncture of the pancreatic duct, followed by wire passage into the jejunum and intraluminal retrieval of the wire by another endoscope

for an attempted endotherapy via the pancreatojejunal anastomosis. A total of 26 patients, with a median age of 55.5 years, underwent 30 EUS procedures. The procedures occurred at a median of 933 days (range, 128–180) following either PD (n=9) or PPPD (n=17). Indications for the procedure included suspected anastomotic stricture (n=13), stricture with filling defects (n=3), stricture and stones (n=6), impacted main pancreatic duct stents (n=2), and acute recurrent pancreatitis (n=6). Endoscopic retrograde cholangiopancreatography had failed once in 16 patients and twice in 2 patients prior to EUS and had not been previously attempted in 12 patients.

The EUS-guided pancreatogram was successful in all 30 procedures, and wire passage across the pancreatojejunal anastomosis was successful in 16 (54%). The wire was successfully grasped in 9 (30%) procedures, with successful retrieval of the wire and pancreatic endotherapy.

Complications included a needle fracture and a peripancreatic abscess. In a univariate analysis, no differences were observed between cases that did or did not have successful wire passage into the jejunum. Short-term clinical success, defined as pain relief up to 6 months after the procedure, was achieved in all 9 procedures in which pancreatic endotherapy was successful. Of 21 patients who had an unsuccessful EUS-guided wire retrieval, 2 patients improved after endoscopic pancreatogastrostomies, 15 were referred for surgery, 2 had celiac plexus blocks, and 2 were lost to follow-up.

Single-Center Retrospective Study Sheds Light on Recurrence Rate of Previously Resected Large Polyps

Endoscopic mucosal resection (EMR) appears to be a safe and generally effective procedure for removal of large (>2 cm) and difficult-to-remove colorectal polyps and was associated with a very low risk of local recurrence, according to Niket Sonpal from the Lenox Hill Hospital in Hauppauge, New York. Sonpal reported findings of a retrospective review of recurrence rates of colorectal polyps during a poster session at the 2012 Annual Meeting of the American College of Gastroenterology (Abstract #P1469). The review sought to determine the recurrence rate of colorectal polyps after removal of large polyps by advanced polypectomy and EMR.

A total of 262 patients whose mean age was 66 years were identified from an endoscopy database and patient records. It was determined that a failed attempt at polyp removal was made by the referring gastroenterologist in 47 (18%) of these patients. Polyps were successfully removed in the remaining 215 (82%) patients, with a recurrence rate of 5.4%.

In the 47 patients in whom polyp removal failed, 45 (95%) were successfully treated; the remaining 2 patients required subsequent surgical referral.

No immediate complications or hospitalizations were reported. A 2-stage procedure was required for completion in 3 patients. Surveillance colonoscopies were performed at a mean follow-up of 14.7 months. Of the 45 treated patients, 13 (29%) were referred for surgical intervention and resection.

At follow-up, histology revealed invasive cancer in 10 (77%) and tubular adenomas in 3 (23%) of the 13 patients referred for surgery. Eight (61%) of these patients underwent surgery. Six (75%) of these 8 patients had a segmental resection with anastomosis, and 2 (25%) had subtotal and total colectomies.

Bowel Wall Thickening on Radiologic Imaging Warrants Endoscopic Evaluation

The finding of bowel wall thickening on radiologic imaging warrants further endoscopic evaluation, according to Pierre Hindy, of the State University of New York Health Science Center at the University Hospital of Brooklyn. Hindy and colleagues assessed the rate of malignancy, clinically significant pathology, and risk factors in patients with gastrointestinal wall thickening who were undergoing endoscopic evaluation. The findings were reported during a poster session at the 2012 Annual Meeting of the American College of Gastroenterology (Abstract #P1475).

An interim analysis of retrospective imaging (computed tomography and magnetic resonance imaging) data from years 2001 to 2007 was performed. A total of 11,935 patients with the word "thickening" on imaging reports were included in the study. A total of 3,103 cases were reviewed. Gastrointestinal thickening was found in 489 (15.7%) cases (all in male veterans). Endoscopy was performed in 352 (72%) of these cases within 3 months of the imaging findings. Significant pathology was evident on endoscopy in 156 (32%) of these cases, and malignant lesions were observed in 127 (26%).

Using a stepwise approach, the investigators determined the odds of malignancy with adjustment for age, race, body mass index, incidence of diabetes mellitus, cigarette smoking, anemia, and ferritin levels. Patients with malignancy had a higher mean age compared with those without malignancy (70.9 years vs 64.8 years, respectively; $P<.01$). Among those with cancer, 45% of patients were racially white, 36% were black, and 20% were Hispanic. No significant difference was found when comparing patients with or without a cancer diagnosis with regard to either body mass index or diabetes mellitus, however; cigarette smoking carried a significant risk for malignancy (odds ratio [OR], 1.772; 95% confidence interval [CI], 1.116–2.815) as did anemia (OR, 1.598; 95% CI, 1.006–2.538; $P<.05$ for both risk factors). The risk of malignancy also was significantly increased with age (OR, 1.042; 95% CI, 1.022–1.064; $P<.01$).

Presentations in Hepatology

A Clinical Decision Tool May Help Predict Response in Patients Receiving Triple Therapy

Triple therapy consisting of boceprevir plus peginterferon and ribavirin is an effective treatment option for many patients with hepatitis C virus (HCV) infection. However, a number of factors can influence patient response. To explore these factors, a multicenter team developed clinical decision tools to predict HCV undetectability at Week 8 of treatment and sustained virologic response (SVR). The process was described by Scott Devine of Merck in Whitehouse Station, New Jersey, during a poster session at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (Abstract #1842).

Devine and colleagues built logistic regression models to predict HCV undetectability at Week 8 of treatment and SVR. The analysis used data from 1,227 patients from the SPRINT-2, RESPOND-2, and PROVIDE trials of boceprevir. Factors used for the development of the models included prior treatment with peginterferon and ribavirin, interleukin (IL)-28B genotype, HCV genotype 1 subtype, initial ribavirin dose, age, race, sex, HCV RNA level after 4 weeks of peginterferon and ribavirin therapy, $\log_{10}$ reduction in HCV RNA levels from baseline to Week 4, and baseline characteristics (weight, body mass index [BMI], hemoglobin level, fibrosis score, the ratio between alanine aminotransferase [ALT] level and the upper limit of normal, platelet count, statin use, steatosis score, and HCV RNA level). Final models that included baseline variables plus HCV RNA level at Week 4 were developed to predict response at Week 8 (n=856) and SVR (n=522). Both models included treatment-naïve patients, relapsers, and partial and prior nonresponders.

A step-down approach was used to reduce the final number of predictors. In the model to predict response at Week 8, the final variables were race, initial ribavirin dose, platelet count, $\log_{10}$ reduction in HCV RNA level from baseline to Week 4, and HCV RNA level at Week 4. In the SVR model, the final factors were sex, BMI, ribavirin use, platelet count, HCV genotype 1 subtype, and HCV RNA level at Week 4. The final model calibration curves had good discrimination for both the Week-8 response and SVR models (C-statistics, 0.89 and 0.83, respectively). In addition to successfully predicting response at Week 8 and SVR without invasive testing, these nomograms could also be useful for clinical decision-making about the initiation and maintenance of therapy.

Ritonavir's PK Effect on Boceprevir in HCV/HIV Coinfection May Not Compromise Boceprevir Efficacy

Administration of ritonavir-boosted HIV protease inhibitors reduces boceprevir concentrations in healthy volunteers. To further explore this interaction, Larissa A. Wenning of Merck, Whitehouse Station, New Jersey, and colleagues assessed boceprevir pharmacokinetics (PK) in patients coinfected with hepatitis C virus (HCV) and HIV. The study also evaluated the relationships among boceprevir PK and pharmacodynamics (PD), sustained virologic response (SVR), and anemia. These data were presented during a poster session at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (Abstract #770).

Data from a phase II HCV/HIV coinfection study, the phase III SPRINT-2 study, and the phase III RESPOND-2 study were analyzed. Data on boceprevir-related PK were available for 51 patients in the coinfection study, 105 patients in SPRINT-2, and 84 patients in RESPOND-2. A population PK model was used to estimate the PK parameters. For the study arms that contained boceprevir, the overall response was estimated using a linear regression model for SVR or anemia, in which boceprevir PK (area under the curve from 0–8 hours [$AUC_{0\text{-}8hr}$] or concentration at 8 hours [C_{8hr}]) were used as predictors.

The cross-study comparison of boceprevir PK found that the boceprevir $AUC_{0\text{-}8hr}$ was approximately 20% lower in the HCV/HIV coinfection study than in the studies of patients monoinfected with HCV. In addition, the C_{8hr} was approximately 27% lower in the coinfection study compared with the monoinfection studies. The SVR and anemia results regarding PK and PD were similar for both boceprevir $AUC_{0\text{-}8hr}$ and C_{8hr}. Thus, Wenning and colleagues were unable to determine whether $AUC_{0\text{-}8hr}$ or C_{8hr} was a better predictor of efficacy or safety. The study also found no significant relationship between boceprevir PK and SVR rates. However, there was a lower probability of anemia (hemoglobin level of 8.5–10 g/dL) with decreasing boceprevir PK, although this result was not significant for the coinfection study data alone.

The investigators concluded that overall boceprevir exposure was reduced in patients coinfected with HCV/HIV compared with patients monoinfected with HCV. However, reduced boceprevir exposure is unlikely to adversely influence the efficacy of treatment, given that

the relationship between boceprevir PK and SVR rates was not significant. Although reduced boceprevir exposure was associated with a reduced probability of anemia, data on ribavirin PK were not collected in the coinfection study, which showed no relationship between boceprevir PK and ribavirin dose; however, ribavirin cannot be eliminated as a confounding factor in the analysis.

The Second-Generation HCV NS3/4A Protease Inhibitor MK5172 Retains Potent In Vitro Activity Against Boceprevir-Resistant Genotype 1 HCV Isolates

The second-generation hepatitis C virus (HCV) NS3/4A protease inhibitor MK5172 demonstrated activity against multiple HCV genotypes and has been shown to significantly reduce viral load in patients with genotype 1 HCV infection, according to Robert A. Ogert, from Merck Sharpe & Dohme in Kenilworth, New Jersey, who presented study findings during a poster session at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (Abstract #1724). The study sought to confirm the activity of MK5172 against HCV isolates from patients who were clinically resistant to boceprevir. Ogert and coinvestigators amplified the *NS3* gene of 13 different clinical isolates from patients who failed therapy with boceprevir plus peginterferon and ribavirin. The amplified *NS3* genes were then tested against MK5172 using an in vitro, replicon-based phenotypic assay. The resistant isolates also were tested against boceprevir, telaprevir, and simeprevir.

Six genotype 1a isolates and 8 genotype 1b isolates with boceprevir-resistance–associated variants were grouped according to virologic response. There were 8 isolates from patients with incomplete virologic response (3 genotype 1a, 5 genotype 1b), 4 isolates from patients who experienced virologic breakthrough (1 genotype 1a, 3 genotype 1b), 1 relapser (genotype 1a), and 1 nonresponder (genotype 1a). Viral load plots that indicated the presence of resistance-associated variants were presented based on these groupings.

Among patients with incomplete virologic response, the resistance-associated variants in genotype 1a isolates were V36M, T54S, R155K, R155K/T, and A156S, while the variants in genotype 1b isolates were T54A/S, T54A, V170A, T54S, and R155K. Among patients in whom virologic breakthrough occurred, the resistance-associated variant in the genotype 1a isolate was R155T, and the resistance-associated variants in the genotype 1b isolates were V55A, T54A, V170A, and M175L. The variants present in the patient with genotype 1a who relapsed were T54S and R155K, while the patient who was a nonresponder had V36M and R155K variants.

The isolates from patients with genotype 1a who failed boceprevir-based therapy demonstrated in vitro resistance to boceprevir, telaprevir, and simeprevir. An 8–13-fold (boceprevir), 18–36-fold (telaprevir), and greater-than-10-fold (simeprevir) shift in the half maximal inhibitory concentration (IC_{50}) from baseline was observed. The boceprevir failure genotype 1a isolates that were resistant to boceprevir, telaprevir, and simeprevir were responsive to MK5172 (IC_{50}, 0.6–4.4 nM).

Compared with baseline isolates, the isolates from patients with genotype 1b who failed boceprevir were resistant to boceprevir (2.7-fold shift in IC_{50}) and telaprevir (2.8-fold shift in IC_{50}). In contrast to the boceprevir failure genotype 1a isolates, the majority of genotype 1b isolates remained sensitive to simeprevir. Similar to the boceprevir failure genotype 1a isolates, the boceprevir failure genotype 1b isolates were sensitive to MK5172 (IC_{50}, 0.04 –0.25 nM) and had a greater-than-2-fold shift in IC_{50} from baseline. Ogert noted that further studies are underway, including a clonal sequence analysis and deep sequencing of select patient samples.

OPTIMIZE Results Show Noninferiority of Telaprevir Twice Daily Compared with 3 Times Daily

The OPTIMIZE trial, the first phase III clinical trial comparing twice-daily administration of telaprevir with 8-hour administration, met its primary endpoint of showing noninferiority in sustained virologic response at Week 12 (SVR_{12}) rates for twice-daily versus 8-hour dosing of telaprevir in combination with peginterferon and ribavirin. The findings were presented by Maria Buti, of the Hospital General Universitari Vall d'Hebron and Ciberehd in Barcelona, Spain, in a late-breaker poster at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (Abstract #LB-8).

A total of 740 treatment-naïve patients with genotype 1 hepatitis C virus (HCV) infection were randomly selected to receive 12 weeks of peginterferon (180 µg/week) and ribavirin (1,000–1,200 mg/day) plus telaprevir at either 1 of 2 dosages: 750 mg every 8 hours or 1,125 mg every 12 hours. All patients then received peginterferon and ribavirin without telaprevir for an additional 12 or 36 weeks. The total treatment duration was 24 or 48 weeks. Administration of telaprevir was halted if HCV RNA levels were greater than 1,000 IU/mL at Week 4 or if HCV RNA levels were at or above 25 IU/mL at Weeks 12, 24, 32, or 40. Patients were followed until Week 72.

Twice-daily telaprevir was found to be noninferior to telaprevir administered every 8 hours (SVR_{12}, 74% vs 73%, respectively; 95% confidence interval, -4.9–12). A subgroup analysis based on liver fibrosis status and

interleukin (IL)-28B genotype also demonstrated similar SVR_{12} rates for both dosing regimens. Among cirrhotic patients, SVR_{12} rates were 54% for patients who received telaprevir at a dosage of 1,125 mg twice daily versus 49% for those who received telaprevir at a dosage of 750 mg every 8 hours. In noncirrhotic patients, SVR_{12} rates were 78% and 77% for twice-daily versus every-8-hour dosing of telaprevir, respectively. In addition, rapid virologic response (RVR) rates were similar for both dosing regimens (69% and 67%, respectively). In patients who achieved RVR, SVR rates were 86% and 85% for twice-daily versus every-8-hour dosing of telaprevir; in patients who did not achieve RVR, the SVR rate was 47% with either dosing regimen. Relapse rates were 8% for patients who received 1,125 mg of telaprevir twice daily and 7% for patients who received 750 mg of telaprevir every 8 hours. Both dosing regimens had an on-treatment virologic failure rate of 10%.

The safety and tolerability of telaprevir were similar in patients receiving 1,125 mg twice daily and those receiving 750 mg every 8 hours. The most common adverse events in both groups were fatigue, pruritus, anemia, nausea, rash, and headache. Serious adverse events occurred in 8–9% of patients. Treatment discontinuation due to adverse events occurred in 15% of patients who received 1,125 mg of telaprevir twice daily and 19% of patients who received 750 mg of telaprevir every 8 hours. Because the safety profiles and SVR rates were similar for both treatment arms, Buti and her coinvestigators concluded that telaprevir given at a dosage of 1,125 mg twice daily plus peginterferon and ribavirin could offer a safe, effective, and simplified treatment option for patients with genotype 1 HCV infection.

Interim Study Results Show Promise for Telaprevir in Patients with HCV Infection and Severe Fibrosis or Compensated Cirrhosis

Interim results of HEP3002—an ongoing, international, early-access program for patients infected with genotype 1 hepatitis C virus (HCV) with severe fibrosis or compensated cirrhosis—suggest that telaprevir has value in this patient population. Results from the 609 patients of the more than 1,900 patients enrolled in the study were presented by Massimo Colombo of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico at the University of Milan, Italy, in a late-breaker poster at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (Abstract #LB-15).

Enrollment criteria included genotype 1 HCV infection, severe fibrosis, or compensated cirrhosis (Metavir score of F3 or F4), and a platelet count of more than 90,000 cells/mm^3. The mean age of the patients was 53.5 years, 67% of the patients were men, and 98% were white. In addition, 66% of patients had HCV RNA levels of at least 800,000 IU/mL, 45% of patients had severe fibrosis, 55% had cirrhosis, and 28% had genotype 1a HCV infection. At baseline, 20% of patients were treatment-naïve, 28% were prior relapsers, 15% were partial prior responders, 29% were prior null responders, 3% were nonresponders for unspecified reasons, and 5% had prior viral breakthrough.

Patients were treated with telaprevir (750 mg every 8 hours) plus peginterferon and ribavirin for 12 weeks. Peginterferon and ribavirin were then administered for an additional 12–36 weeks using a response-guided treatment paradigm. At Week 4, 329 (54%) patients had undetectable HCV RNA levels. By Week 12, 481 (79%) patients had undetectable HCV RNA levels. The percentage of patients who showed an HCV RNA response at Week 12 was lower for prior null responders (73%) than for prior relapsers or treatment-naïve patients (85% for both groups).

Grade 1–4 anemia developed in 359 (59%) patients, with severe anemia occurring in 31%. Grade 1–4 rash developed in 256 (42%) patients, with severe rash occurring in 4% of patients. Discontinuation due to adverse events occurred in 14% of patients (12% of patients with F3 fibrosis and 16% of patients with F4 fibrosis). Reasons for discontinuation included rash (5%), anemia (3%), asthenia (1%), abdominal pain (1%), nausea (1%), pruritus (1%), and vomiting (1%). The investigators noted that the rates of discontinuation for rash and anemia were similar to those observed in the phase III registration trials for telaprevir. Three cirrhotic patients (0.5%) died during the peginterferon and ribavirin phase of therapy due to hepatic failure/ischemic colitis and multiorgan failure; 1 of these deaths was deemed to be treatment-related, and 1 death was possibly treatment-related.

Long-Term Tenofovir DF for Chronic Hepatitis B Appears to be Safe, Well Tolerated, and Associated with Sustained Response

Six-year results from 2 ongoing 8-year studies demonstrate that tenofovir disoproxil fumarate (tenofovir DF) has good safety and tolerability profiles and is associated with sustained response, according to Patrick Marcellin, of the Hôpital Beaujon in Clichy, France. Marcellin reported these findings at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (Abstract #374).

Patients were randomly selected for treatment with either tenofovir DF or adefovir dipivoxil for 48 weeks in a double-blind comparison, after which those who underwent a liver biopsy were permitted to continue with open-label tenofovir DF for 7 additional years. Monitoring for adverse events and hepatitis B virus (HBV) DNA

occurred every 3 months, resistance surveillance was performed annually, and annual bone mineral density assessments of the spine and hip were added starting at Year 4.

Of the initial 641 patients treated, 585 (93%) entered into the tenofovir DF extension phase and 477 (73%) remained on study at Year 6.

In the long-term evaluation analysis set, in which missing patients were counted as failures, 281 (81%) of 345 patients who were hepatitis B e antigen (HBeAg)-negative and 157 (62%) of 251 patients who were HBeAg-positive had HBV DNA levels of less than 400 copies/mL. Comparable percentages for patients in the on-treatment analysis set, in whom HBV DNA levels of less than 400 copies/mL, were achieved in 283 (~100%) of the 284 patients who were HBeAg-negative and 167 (99%) of the 169 patients who were HBeAg-positive. In the on-treatment analysis set, 228 (86%) of 265 patients who were HBeAg-negative and 127 (78%) of 162 patients who were HBeAg-positive showed normalization of alanine aminotransferase levels. Half of the patients who were HBeAg-positive showed loss of HBeAg, and 61 (37%) of 163 patients who were HBeAg-positive had HBeAg seroconversion.

Over the 6-year follow-up, tenofovir DF proved to be well tolerated, with fewer than 2% of patients discontinuing due to an adverse event. A confirmed renal event occurred in 1.5% or fewer patients. Over 2 years, bone mineral density levels remained stable. Importantly, no tenofovir DF resistance was detected through Year 6.

Tenofovir DF Is Safe and Effective in Patients with Chronic Hepatitis B Virus Infection Resistant to Lamivudine

Tenofovir disoproxil fumarate (tenofovir DF) was shown to suppress hepatitis B virus (HBV) DNA without signs of emerging drug resistance in patients with documented resistance to lamivudine, reported Scott Fung of the Toronto General Hospital in Ontario, Canada, during a presentation at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (Abstract #20). Fung and colleagues conducted a randomized, double-blind, phase IIIb trial that compared tenofovir DF (n=141) with emtricitabine plus tenofovir DF (n=139; given as a fixed-dose combination tablet). All patients had chronic HBV and documented lamivudine resistance, with 103 or more HBV DNA copies/mL at the time of study screening despite receiving lamivudine. At the time of study entry, patients were stratified by alanine aminotransferase (ALT) levels and hepatitis B e antigen (HBeAg) status.

The majority of patients in both the tenofovir DF and emtricitabine/tenofovir arms completed the 96-week study period (94% and 90%, respectively). At Week 96, a similar proportion of patients in the tenofovir DF and the emtricitabine/tenofovir DF arms had less than 400 HBV DNA copies/mL (89% and 86%, respectively). Normalized ALT levels were present in 44 (62%) of 79 patients in the tenofovir DF and 52 (63%) of 83 patients in the emtricitabine/tenofovir DF arm, and normal ALT levels were achieved in 70% of both arms.

Among HBeAg-positive patients, HBeAg loss occurred in 10 (15%) of 65 patients treated with tenofovir DF and 9 (13%) of 68 patients treated with emtricitabine/tenofovir DF. HBeAg seroconversion occurred in 7 (11%) of 65 patients in the tenofovir DF monotherapy group and 7 (10%) of 68 patients in the emtricitabine/tenofovir DF group.

Both treatments were well tolerated, with only 1% of patients discontinuing therapy due to an adverse event. There were no confirmed cases of increased levels of serum creatinine (≥0.5 mg/dL from baseline). Serum phosphorous levels below 2 mg/dL occurred in 1% of patients, and reduced creatinine clearance (<50 mL/min) occurred in 3% of patients. No clinically relevant bone loss or nontraumatic bone fractures were observed. Over the 96-week study period, no tenofovir DF resistance was observed.

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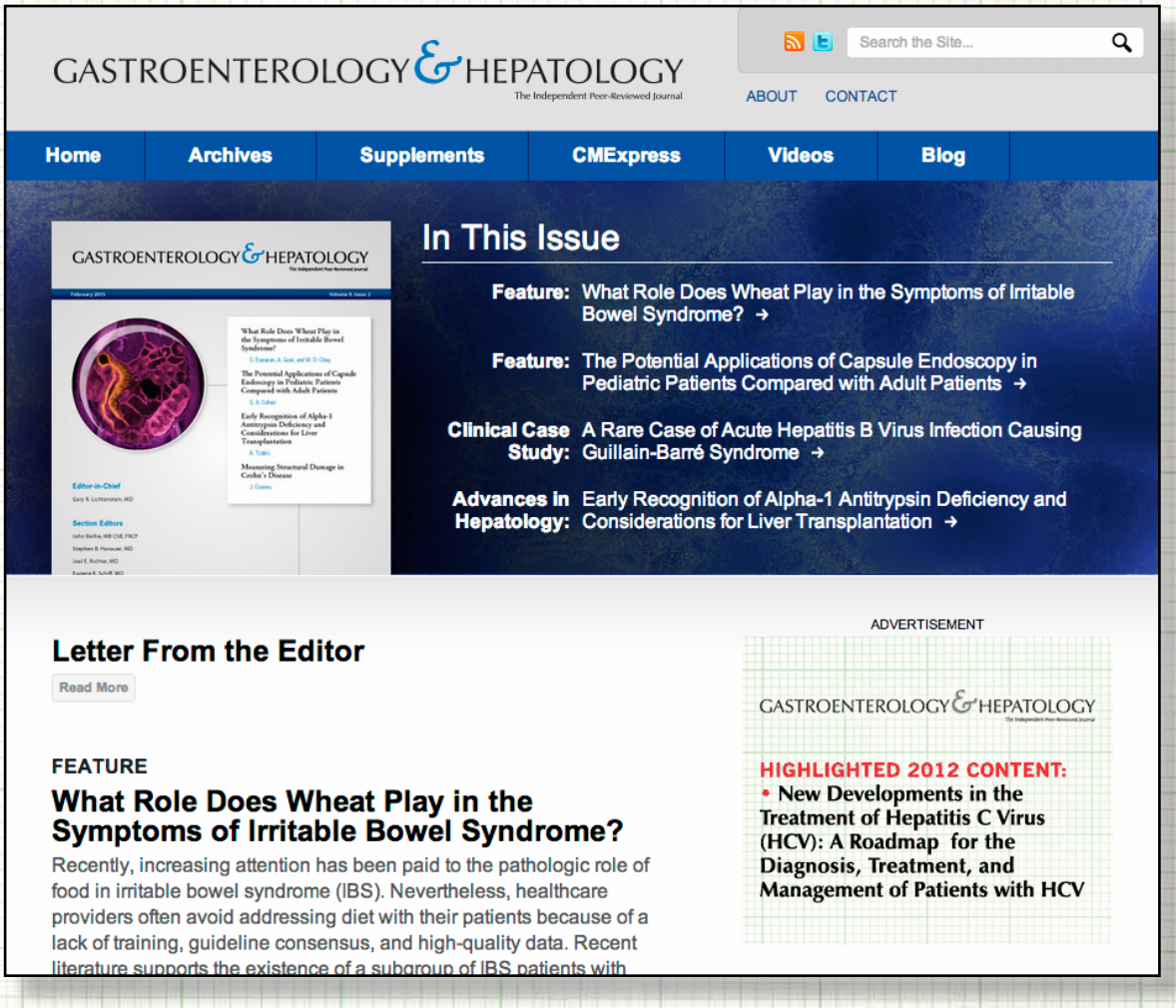

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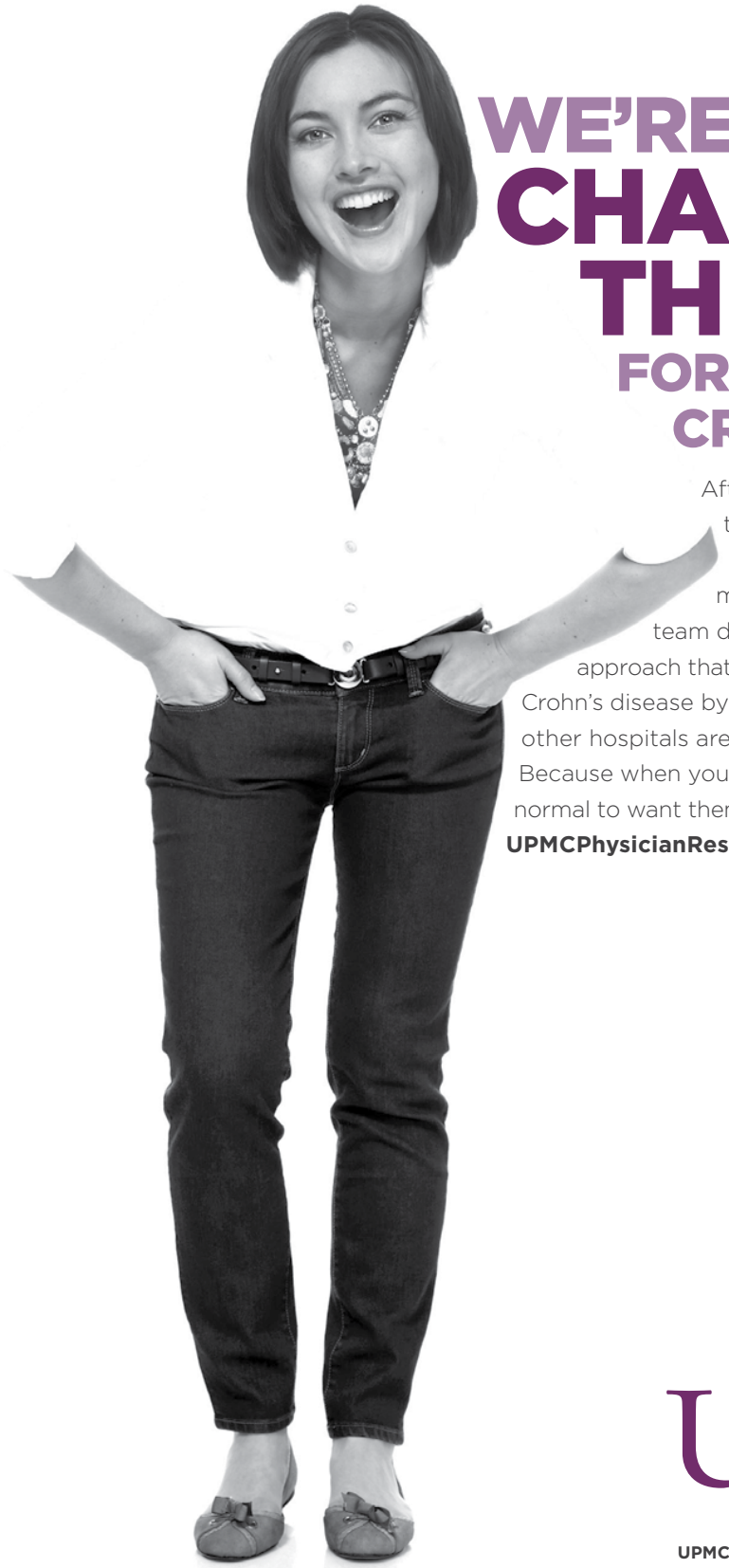

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