



PRODUCT PROFILER

Remicade[®]

INFLIXIMAB

A Chimeric Monoclonal Antibody Against Tumor
Necrosis Factor

FDA-Approved Indications:

- Rheumatoid Arthritis
- Crohn's Disease
- Pediatric Crohn's Disease
- Ankylosing Spondylitis
- Psoriatic Arthritis
- Ulcerative Colitis
- Plaque Psoriasis

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THE PRODUCT PROFILER

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

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DISCLOSURE

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Infiximab: A Chimeric Monoclonal Antibody Against Tumor Necrosis Factor

INTRODUCTION

The volume of information about the human immune system has rapidly increased over the past 10 years, thereby promoting a better understanding of normal immune system function as well as an identification of the role of immune system dysfunction.¹ To adequately evaluate and treat the immune system in disease processes, it is vital to understand its normal functions and to recognize the signs and symptoms of immune dysfunction.

The immune system serves primarily to protect the body against infection. To accomplish this feat, it must recognize infection, replicate itself, mobilize its defenses, and retain a memory of past infections. To maintain normal health, the immune system is required to demarcate “self” from “non-self” in order to prevent damage to its host. Unfortunately, in the five disease states that will be discussed in the following pages, the immune system is unable to make that distinction and thus inevitably attacks various organs and tissues in the host, causing inflammation and damage. In this Product Profiler, we will provide a review of the evidence-based literature supporting the FDA-approved indications for infliximab (IFB) in the treatment of rheumatoid arthritis, Crohn’s disease in adults and children, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, and plaque psoriasis.

Rheumatoid arthritis (RA) is the most common systemic inflammatory disease that is characterized by symmetrical joint involvement.² Extra-articular involvement, including rheumatoid nodules, vasculitis, eye inflammation, cardiopulmonary disease, and splenomegaly, is a manifestation of this disease. Although RA is chronic in nature, some patients may experience periods of remission. In healthy persons, mediators aid and disengage an inflammatory response; in patients with RA, however, an imbalance of these mediators is typical and usually results in the destruction of cartilage and bone in the joints. The estimated prevalence of RA is 1% to 2% in the U.S. population, and there is no predilection for its occurrence in a specific race.

Crohn’s disease (CD), a form of inflammatory bowel disease, is an idiopathic transmucosal process of the gastrointestinal (GI) tract.³ Although the terminal ileum is most commonly affected, CD may involve any part of the GI tract, from the mouth to the anus. Most often, the entire bowel wall is injured and the mesen-

tery may become thickened and fibrotic. Complications may include the formation of fistulas, arthritis, skin lesions, kidney stones, and bowel obstruction; patients with bowel obstruction may require surgery. The prevalence of Crohn’s disease (CD) is approximately 5 in 100,000 people in the U.S. and 50 in 100,000 people in other Westernized countries.⁴ Women and men appear to be affected equally.

Ankylosing spondylitis (AS) is a rheumatic disease that usually results in arthritis of the spine and sacroiliac joints. It may cause inflammation of the eyes, lungs, and heart valves.⁵ Symptoms may be noted as intermittent episodes of back pain that progress into a chronic disease that affects the spine and peripheral joints or other body organs, resulting in loss of motion and deformity. AS affects approximately 129 of 100,000 individuals in the U.S. and typically strikes adolescents and young males. The incidence seems to vary by ethnic group, and the disease occurs most commonly in Native Americans.

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis of the skin. The prevalence of psoriasis ranges from 1% to 3%, and 10% to 30% of patients with psoriasis develop psoriatic arthritis.^{6,7} In the U.S., approximately one million adults have psoriatic arthritis.

Ulcerative colitis (UC) is a debilitating chronic disease affecting 250,000 to 500,000 Americans, for whom there is no pharmacological cure.⁸ Characterized by diffuse inflammation and ulceration of the inner lining of the colon, symptoms can include unwanted weight loss, severe—sometimes uncontrollable—bloody diarrhea with rectal urgency and tenesmus; fatigue; and frequent abdominal pain. For some patients, symptoms may lead to surgical removal of the colon or to secondary complications such as colorectal cancer.⁸

Psoriasis (PsO) is an immune-mediated, chronic inflammatory disease in which portions of the skin are affected with erythematous plaques^{9,10} and covered by silvery-white scales.¹¹ The extent of skin involvement can range from discrete, localized areas to generalized body involvement. The joints and nails may also be affected with the disease. Psoriasis affects approximately 5.8 to 7.5 million patients, and nearly one-fourth of PsO patients have moderate-to-severe psoriasis.⁷ From 150,000 to 250,000 new cases are diagnosed annually.¹¹

PATHOPHYSIOLOGY

In the inflammatory process, white blood cells, primarily CD4-positive ones, infiltrate the synovium and subsequently kindle the monocytes, macrophages, fibroblasts, and B cells.¹² Afterward, activated B cells begin to produce immunoglobulins, including rheumatoid factor, which, consequently, might not be present in all patients.

Simultaneously, the monocytes and macrophages manufacture cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α). TNF- α activates the endothelial cells in the synovium, which express adhesion molecules on their surface and increase the permeability of the endothelial layer, thereby promoting the recruitment of more inflammatory cells into the joints.

TNF- α and IL-1 are potent stimulators of mesenchymal cells, such as synovial fibroblasts, osteo-

clasts, and chondrocytes, which are important in the release of tissue-destroying matrix metalloproteinases. TNF- α may also have a prominent role in stimulating the production of IL-1, IL-6, and granulocyte–monocyte colony-stimulating factor.

TNF- α is a key proinflammatory cytokine in patients with CD, but it is also found in increased concentrations in the blood, colonic tissue, and stools of patients with UC.¹³

In psoriasis, numerous studies have identified TNF- α as a particularly relevant cytokine regulating the complex inflammatory cascade. Its key role is underlined by the therapeutic efficacy of compounds that interfere with TNF- α functions.¹¹

The aforementioned processes are key components in the pathophysiology and progression of the diseases discussed here, and thus TNF- α appears to be an appropriate target for drug therapy.

Chemistry and Clinical Pharmacology

CHEMICAL AND PHYSICAL PROPERTIES¹⁴

Infliximab (IFB, REMICADE[®], Centocor), a chimeric human–murine (mouse) immunoglobulin (IgG_{1-κ}) monoclonal antibody, is composed of human constant and murine variable regions. Its molecular weight is approximately 149,100 daltons.

PHARMACOLOGY AND MECHANISM OF ACTION¹⁴

IFB binds specifically to TNF- α and neutralizes its biological activity as a pro-inflammatory cytokine. By binding to the soluble and transmembrane forms of TNF- α , it inhibits the binding of TNF- α to its p55/p75 receptors. TNF- α is involved in the pathogenesis of numerous conditions, such as RA, CD, UC, AS, PsA, and PsO.

IFB does not neutralize TNF- β (lymphotoxin α), a related cytokine that utilizes the same receptors as TNF- α . Biological activities attributed to TNF- α include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, and induction of acute-phase reactants and other liver proteins, as well as tissue-degrading enzymes produced by synoviocytes and/or chondrocytes.

Cells expressing transmembrane TNF- α bound by IFB can be lysed *in vitro* or *in vivo*. IFB inhibits the functional activity of TNF- α in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes, and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which IFB exerts its clinical effects is unknown. Anti-TNF- α antibodies reduce disease activity in the cotton-top tamarin colitis model and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. IFB prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of TNF- α and, when administered after disease onset, allows eroded joints to heal.

PHARMACODYNAMICS¹⁴

Elevated concentrations of TNF- α have been found in involved tissues and fluids of patients with RA, CD, UC, AS, PsA, and PsO.

In RA, treatment with IFB reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction (IL-8 and monocyte chemoattractant protein [MCP-1]) and tissue degradation (matrix metalloproteinase [MMP] 1 and 3).

In Crohn's disease, treatment with IFB reduced infiltration of inflammatory cells and TNF- α production in inflamed areas of the intestine, and it reduced the proportion of mononuclear cells from the lamina propria able to express TNF- α and interferon. After treatment with IFB, patients with RA or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared with baseline levels. Peripheral blood lymphocytes from IFB-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared with cells from untreated patients.

In PsA, treatment with IFB resulted in a reduction in the number of T cells and blood vessels in the synovium and psoriatic skin as well as a reduction of macrophages in the synovium. In plaque psoriasis, IFB treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which IFB exerts its clinical effects is unknown.

PHARMACOKINETICS¹⁴

In adults, single intravenous (IV) infusions of 3 to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at the steady state was independent of the dose and indicated that IFB was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in RA, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the terminal half-life of IFB is 7.7 to 9.5 days.

Following an initial dose of IFB, repeated infusions at two and six weeks resulted in predictable concentration-time profiles following each treatment. No systematic accumulation of IFB occurred upon continued repeated treatment with 3 or 10 mg/kg at four- or eight-week intervals. Development of antibodies to IFB increased IFB clearance.

PRODUCT PROFILER: Infliximab

At eight weeks, after a maintenance dose of 3 to 10 mg/kg of IFB, median IFB serum concentrations ranged from approximately 0.5 to 6 mcg/ml; however, IFB concentrations were not detectable (<0.1 mcg/ml) in patients who became positive for antibodies to IFB. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or sex. It is not known whether there are

differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

IFB peak and trough concentrations were similar in pediatric (aged 6 to 17 years old) and adult patients with Crohn's disease following the administration of the recommended regimen (See Dosage and Administration, page 40).

Clinical Trials and FDA-Approved Indications

RHEUMATOID ARTHRITIS

Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy: ATTRACT

Disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate (MTX), have become the standard medication of choice in treating RA either as monotherapy or in combination with other DMARDs such as gold salts, penicillamine, and hydroxychloroquine. In some cases, associated side effects are intolerable, and these medications are not always efficacious in providing a therapeutic response.¹⁵

Trial Description

ATTRACT, a placebo-controlled, double-blind, randomized trial, analyzed the use of IFB in individuals whose disease was inadequately controlled with MTX therapy.¹⁵ The investigators added IFB to the therapeutic doses of MTX to evaluate its safety and efficacy in relieving the signs and symptoms of RA.

Four hundred twenty-eight patients with active RA were enrolled in this international phase 3 clinical trial. Figure 1 illustrates the dosing in randomized study groups for the trial.

Outcomes were assessed at Weeks 30, 54, and 102. Patients had to meet specified laboratory screening cri-

teria before they were deemed eligible to enroll. Patients were excluded if they:

- had little or no ability for self-care.
- had any current inflammatory conditions.
- were using DMARDs other than MTX.
- had other infections or diseases, malignant or benign, except basal cell carcinoma, within the past five years.

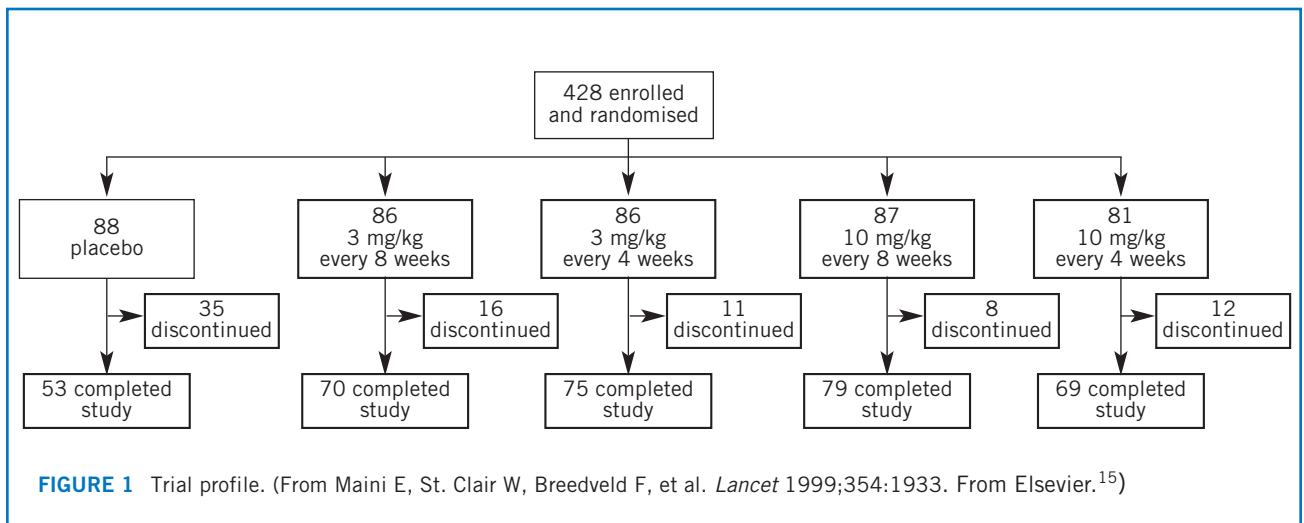
Trial Endpoints and Methods

30 Weeks: Maini et al., 1999¹⁵

The primary endpoint at 30 weeks was prospectively defined as 20% improvement according to the ACR 20 assessment without requiring a surgical joint procedure (i.e., arthrodesis and joint replacement), initiation of new drugs, or increases in the doses of medication. Patients received their baseline doses of MTX or corticosteroids during the trial.

Secondary measurements of response to therapy included documentation of 50% and 70% improvement (ACR 50 and ACR 70), reduction in individual measurements of disease activity, and a general health assessment.

Pharmacokinetics and human antichimeric antibody formation, in addition to anti-double-stranded DNA (anti-dsDNA) antibodies and rheumatoid (Rh) factors, were measured throughout the duration of the trial.



Patients who had received continuous MTX for at least three months and at stable doses for at least four weeks were randomly assigned to one of five treatment groups: placebo (0.1% human serum albumin, except in France, where normal saline was used to comply with government regulations) or one of four IFB treatment regimens: 3 mg/kg every four weeks, 3 mg/kg every eight weeks, 10 mg/kg every four weeks, or 10 mg/kg every eight weeks. All patients received IV infusions at Weeks zero, two, and six over two-hour periods. Patients were assessed every four weeks for 30 weeks.

Baseline characteristics were well matched. The population of patients was predominantly white, female, and positive for the Rh factor. The median age range was 51 to 56 years, and the duration of disease was 7.2 to 9 years.

54 Weeks: Lipsky et al., 2000¹⁶

Lipsky and colleagues attempted to determine to what extent repeated doses of IFB and MTX would control the clinical manifestations of RA over a one-year period. Radiographic progression was the primary endpoint at 54 weeks.

The methods were identical to those used at 30 weeks; ACR 20, ACR 50, and ACR 70 responses were assessed at 54 weeks. Serological analyses for anti-nuclear antibodies (ANAs) and anti-dsDNA antibodies were measured at baseline at the second, fourth, sixth, and 10th week and every eight weeks thereafter.

The investigators used radiographic assessment to determine the extent of damage to cartilage and bone. They assessed the effect of therapy on joint damage on the basis of an evaluation of radiographs of the patients' hands and feet for erosions and joint-space narrowing. The van der Heijde modification of the Sharp scoring system was used to record the scores. The scores on this scale ranged from 0 to 440, with higher scores indicating more joint damage. Radiographs were obtained at baseline and after 30 and 54 weeks.

The investigators determined the overall effect of treatment by evaluating the difference in the means or proportions between the groups. Pairwise comparisons of the IFB and placebo groups were made when the overall effect of treatment had a positive effect on the primary endpoint. All statistical tests were two-sided.

102 Weeks: Maini et al., 2004¹⁷

Physical function was the primary endpoint at 102 weeks. In addition to evaluating the ACR 20 criteria, investigators analyzed the ability of IFB-MTX to provide a sustained benefit in physical function, as assessed by the HAQ, a self-administered form that examined functional ability. The HAQ was administered every four weeks and used a scale ranging from 0 (no difficulty) to 3 (unable to perform the activity). This tool analyzed a

variety of areas, including the ability of the participants to dress, arise, eat, walk, reach, grip, and maintain personal hygiene. Positive values indicated a decrease in arthritis-related functional ability from baseline measures.

Prolonged improvement in signs and symptoms and inhibition of radiographic progression over two years was also evaluated, and the Short-Form 36 Health Survey Questionnaire (SF-36) was used to assess health-related quality of life.

Of the initial 428 patients, 259 (61%) patients entered the second year of treatment; 216 (83%) continued to receive IFB-MTX for 102 weeks. The trial protocol was continued as stated previously.

Results

30 Weeks: Maini et al., 1999¹⁵

IFB proved efficacious, as evaluated by the primary efficacy measurement (the ACR 20 response), when compared with placebo.

At 30 weeks, all groups responded rapidly; more than 50% of the responders attained the ACR 20 criteria by the first evaluation at two weeks, with approximately 90% attaining it at the six-week evaluation. Thereafter, total response rates were sustained at levels between 50% and 60% up to the 30-week endpoint.

Thirty-five of 88 (36%) patients in the placebo group discontinued therapy, which was a significantly higher number than in the IFB group (8–16 patients, or 9%–18%).

Overall, a significantly greater percentage of IFB-treated patients achieved a more substantial response, as defined by ACR 50 and ACR 70 criteria (Table 1). In addition, the median titer of Rh factor declined in the IFB-treated groups, with no change seen with placebo.

To assess the magnitude of individual clinical responses, the investigators calculated the percentage reduction at 30 weeks from baseline. For several indices, the values showed a trend toward improvement in placebo-treated patients, but these changes were small, compared with the improvement recorded with IFB.

Pharmacokinetic measurements were made in 197 patients. The half-life of IFB was 8 to 12 days, consistent with mainly an intravascular distribution. Human antichimeric antibody formation could not be measured in most patients receiving IFB because serum IFB interferes with the assay. However, of 27 IFB-treated patients who discontinued treatment before 30 weeks, three tested positive for human antichimeric antibodies (two with a titer of 1/10 and one with a titer of 1/40).

For more details on adverse reactions, see the Safety Considerations discussion on page 11.

54 Weeks: Lipsky et al., 2000¹⁶

Based on the ACR 20, ACR 50, and ACR 70 criteria,

TABLE 1 Patients Achieving American College of Rheumatology (ACR) 50% and 70% Responses at 30 Weeks After Therapy for Rheumatoid Arthritis

Response	Placebo + MTX (n = 84)	Infliximab + Methotrexate (MTX)			
		3 mg/kg q 8 weeks (n = 83)	3 mg/kg q 4 weeks (n = 85)	10 mg/kg q 8 weeks (n = 85)	10 mg/kg q 4 weeks (n = 80)
ACR 50	4 (5%)	22 (27%)	25 (29%)	26 (31%)	21 (26%)
<i>P</i>		<.001	<.001	<.001	<.001
ACR 70	0 (0%)	7 (8%)	9 (11%)	15 (18%)	9 (11%)
<i>P</i>		.007	.002	<.001	.002

* ACR 50 and ACR 70 refer to the level of response to the therapy that achieved 50% and 70% change, respectively, from baseline measures in the swollen and tender joint counts plus at least of five other measurements of disease activity, according to ACR criteria.

From Maini E, St. Clair W, Breedveld F, et al. *Lancet* 1999;354:1937. Reprinted with permission from Elsevier.¹⁵

more patients in the groups receiving IFB plus MTX (IFB–MTX) demonstrated a decline in signs and symptoms at 54 weeks, compared with the group receiving MTX alone. The lowest dose of IFB (3 mg/kg every eight weeks) was significant in achieving ACR 20 improvement (Table 2).

Other results were similar when the individual components of the ACR criteria were analyzed, including the number of swollen and tender joints, the patients' assessment of pain, and serum CRP concentrations. All dosages of IFB–MTX were superior to MTX and placebo (*P* < .001; in the case of pain, *P* = .016 [when

3 mg/kg was administered every eight weeks]). In addition, all doses of IFB–MTX resulted in significantly reduced serum Rh factor values (by approximately 40%) at 54 weeks, whereas MTX alone had no significant effect.

The MTX monotherapy group experienced more progression of joint damage from the baseline values, compared with the patients receiving IFB–MTX (Table 3). The patients receiving the combination therapy had a 10% increase in total radiographic scores but showed no significant change in the mean radiographic scores when baseline scores were compared

TABLE 2 Clinical and Laboratory Responses to Infliximab (IFB) + Methotrexate (MTX) Therapy at 54 Weeks

Response	MTX + Placebo (n = 88)	IFB 3 mg/kg q 8 weeks + MTX (n = 86)	IFB 3 mg/kg q 4 weeks + MTX (n = 86)	IFB 10 mg/kg q 8 weeks + MTX (n = 87)	IFB 10 mg/kg q 4 weeks + MTX (n = 81)
ACR criteria					
20% improvement (%)	17	42	48	59	59
<i>P</i>		<.001	<.001	<.001	<.001
50% improvement (%)	8	21	34	39	38
<i>P</i>		.027	<.001	<.001	<.001
70% improvement (%)	2	10	17	25	19
<i>P</i>		.04	.001	<.001	<.001
Decrease in no. of swollen joints	13 ± 61	37 ± 62	50 ± 54	60 ± 38	63 ± 34
<i>P</i>		<.001	<.001	<.001	<.001
Decrease in no. of tender joints	23 ± 63	49 ± 52	55 ± 48	56 ± 52	65 ± 33
<i>P</i>		<.001	.001	<.001	<.001
Serum C-reactive protein (mg/dl)	2.8 ± 3.1	1.6 ± 1.9	1.5 ± 2.5	1.2 ± 1.7	1.1 ± 1.4
<i>P</i>		.006	<.001	<.001	<.001

Plus-minus values are means plus or minus the standard deviation. *P* values are for the comparison with the group given methotrexate and placebo.

From Lipsky P, van der Heijde D, St. Claire, et al. *N Engl J Med* 2000;343:1597. © 2000 Massachusetts Medical Society.¹⁶

TABLE 3 Effect of Treatment on Joint Damage at 54 Weeks in Patients with Rheumatoid Arthritis

Variable	MTX + Placebo (n = 64)	IFB 3 mg/kg q 8 weeks + MTX (n = 71)	IFB 3 mg/kg q 4 weeks) + MTX (n = 71)	IFB 10 mg/kg q 8 weeks) + MTX (n = 77)	IFB 10 mg/kg q 4 weeks) + MTX (n = 66)
Radiographic score					
Total score	7.0 ± 10.3	1.3 ± 6.0	1.6 ± 8.5	0.2 ± 3.6	-0.7 ± 3.8
<i>P</i>		<.001	<.001	<.001	<.001
Erosion score*	4.0 ± 7.9	0.2 ± 2.9	0.3 ± 4.7	0.2 ± 2.9	-0.7 ± 3.0
<i>P</i>		<.001	<.001	<.001	<.001
Joint-space narrowing score†	2.9 ± 4.2	1.1 ± 4.4	0.7 ± 4.3	0.0 ± 3.1	0.0 ± 2.5
<i>P</i>		<.001	<.001	<.001	<.001
Major progression (% of patients)	31	8	13	1	0
<i>P</i>		<.001	<.001	<.001	<.001
Improvement (% of patients)	14	44	48	39	55
<i>P</i>		<.001	<.001	<.001	<.001
Clinical response					
No. of patients	14	35	36	48	44
Total radiographic score†	6.0 ± 8.7	1.5 ± 7.2	0.7 ± 5.5	0.1 ± 3.8	1.4 ± 4.0
<i>P</i>		.017	.009	.006	<.001
No clinical response					
No. of patients	50	36	35	29	22
Total radiographic score†	7.2 ± 10.8	1.1 ± 4.7	2.6 ± 10.7	0.2 ± 3.4	0.7 ± 3.2
<i>P</i>		<.001	<.001	<.001	<.001
Disease duration (≥3 years)					
No. of patients	14	15	16	17	4
Total radiographic score†	9.1 ± 7.7	0.4 ± 4.5	-1.1 ± 6.4	0.6 ± 2.7	0.3 ± 3.3
<i>P</i>		<.001	<.001	<.001	.007

Plus-minus values are means plus or minus standard deviation.

Joint damage was assessed radiographically with use of the van de Heijde modification of the Sharp scoring system. Total scores may range from 0 to 440. Scores from erosion subscale used can range from 0 to 280. Scores on the joint-space-narrowing subscale can range from 0 to 160. Higher scores indicate more articular damage.

P values are for comparison with the group given methotrexate and placebo.

A clinical response was defined as an improvement of at least 20% according to the criteria of the American College of Rheumatology (ACR 20).

* Denotes increase or decrease from baseline.

† Denotes increase from baseline only.

From Lipsky P, van der Heijde D, St. Claire, et al. *N Engl J Med* 2000;343:1597. © Massachusetts Medical Society.¹⁶

with those at 54 weeks. There were no significant differences among the four groups (*P* = .43).

IFB had a significant benefit on erosions and joint-space narrowing, both independently and when the patients' hands and feet were examined separately. In addition, the rate of joint-damage progression was reduced in patients who demonstrated a clinical response to IFB-MTX at 54 weeks. Thirty-one percent of the

patients in the MTX monotherapy group had radiographic evidence of major progression of disease, compared with 0% to 13% of patients receiving IFB-MTX (*P* < .001).

Significantly more patients taking IFB-MTX (39%–55%) had improved radiographic scores after 54 weeks than did those receiving MTX alone (14%).

During this trial, the percentage of patients in whom ANAs and antibodies against dsDNA developed were

significantly higher in the IFB groups than in the group given MTX alone. Of 60 patients who had discontinued treatment before 30 weeks or after 54 weeks, five patients (8%) had serum antibodies against IFB, all at a low titer.

102 Weeks: Maini et al., 2004¹⁷

All clinical responses based on ACR 20 improvement criteria were significantly greater in every IFB–MTX treatment group. This figure also paralleled the clinical responses seen at 30 and 54 weeks.

The group of patients receiving 3 mg/kg every eight weeks showed the smallest improvement; those receiving 10 mg/kg every eight weeks and IFB 3 mg/kg every four weeks achieved the greatest improvements.

Significant changes from baseline were observed in vitality and social functioning subscale scores, but there were no significant differences in the change from baseline of the mental component when compared with any of the groups.

Pairwise comparisons of the total radiographic score showed that the change from baseline to Week 102 in each IFB–MTX treatment group was significantly lower than that in the MTX-only group.

The median change from baseline in the HAQ scores and the physical component of the SF-36 score was significantly greater in patients receiving IFB–MTX than those receiving MTX alone ($P < .001$).

There were significant reductions in both erosion and joint-space narrowing ($P < .001$) for all IFB dosages, except for 3 mg/kg every eight weeks ($P = .002$) in the IFB–MTX patients when compared with the MTX-only treatment groups. In addition, there were fewer newly eroded joints per patient ($P < .001$).

Patients who received each of the four IFB–MTX treatments experienced a significantly greater decrease in CRP levels over 102 weeks in comparison with patients receiving MTX alone.

Safety Considerations at 102 Weeks¹⁷

Adverse drug event (ADE) profiles were similar in all of the treatment groups. Serious ADEs were reported by similar proportions of patients who received MTX only (33%) and IFB–MTX (29%). Approximately 2% of placebo infusions demonstrated an associated reaction compared with 3% of IFB infusions. Infusion reactions led to discontinuation of IFB plus MTX therapy in only eight of the 183 IFB infusions with an associated infusion reaction.

Four patients (5%) who received the MTX-only regimen died during the 102-week trial period. All four deaths were judged not to be related to the trial drug. Seven patients (2%) who were treated with IFB plus MTX died during the trial. In the IFB–MTX treatment groups, patient deaths were attributed to bilateral pulmonary embolism, ruptured abdominal aortic

aneurysm, sepsis, cardiorespiratory arrest associated with disseminated tuberculosis, pulmonary fibrosis, coccidioidomycosis peritonitis, and presumed cardiac arrhythmia. One additional death caused by fatal myocardial infarction occurred after the patient's participation in the trial and was reported during the long-term safety follow-up.

Malignancies were reported in one patient (1%) who received the MTX-only regimen and in nine patients (3%) treated with the IFB–MTX regimens. Three IFB plus MTX-treated patients and two MTX-only-treated patients had malignancies diagnosed during the three-year follow-up period.

From 54 weeks to 102 weeks, there was an increase of approximately 13% in the percentage of patients with ANA in the IFB–MTX group and an increase of about 5% in the percentage of patients with anti-dsDNA antibodies, compared with a 6% increase in the percentage of patients with ANAs and a 0% increase in the percentage of patients with anti-dsDNA in the MTX-only group. Only patients who tested positive for ANA were tested for anti-dsDNA antibodies. No additional cases of lupus-like syndrome were observed in the second year of the trial, and only one patient experienced a lupus-like reaction during the trial.

Eight percent of patients receiving the IFB–MTX regimens developed antibodies to IFB during the trial. Despite the presence of antibodies, similar proportions of patients with antibodies to IFB (40%) and without antibodies to IFB (38%) achieved an ACR 20 response.

Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset: ASPIRE

*St. Clair et al.*¹⁸

ASPIRE was conducted to compare the benefits of initiating treatment in patients with RA for a duration of three years or less.

Trial Endpoints

The co-primary endpoints were reduction of signs and symptoms of RA, inhibition of structural damage, and improvement in physical function.

Methods and Discussion

Only three or fewer pre-trial doses of MTX were allowed so that more patients who might have recently started taking this medication could be eligible to enroll in the trial. MTX-naïve patients with moderately to severely active early RA (more than three months and less than three years from date of diagnosis) were enrolled. The median age of the patients was 51 years, with a median disease duration of 0.6 years and median swollen and tender joint counts of 19 and 31,

respectively. More than 80% of patients had baseline joint erosions.¹⁴

One thousand four (1,004) patients were randomly assigned to one of three treatment groups: MTX–placebo, MTX–IFB 3 mg/kg, or MTX–IFB 6 mg/kg. Oral MTX was started at 7.5 mg/week and was titrated by 2.5 mg/week every one to two weeks to 15 mg/week by the fourth week and to 20 mg/week by the eighth week, along with at least 5 mg/week of oral folic acid. The MTX dosage could be tapered or discontinued only with evidence of toxicity; it was also discontinued if the MTX dose dropped below 7.5 mg/week for four weeks or more. IFB or placebo was given at Week 0, 2, and 6 and every eight weeks thereafter through the 46th week. Oral corticosteroids (10 mg/day or less of prednisone or its equivalent) and nonsteroidal anti-inflammatory drugs (NSAIDs) were maintained at baseline dosages. Other DMARDs were not permitted.

The HAQ and the SF-36 self-evaluation of quality of life were used to evaluate patients’ functional status. Blood samples were obtained to analyze the ESR, serum CRP levels, the presence of ANAs, anti-dsDNA antibodies, and antibodies to IFB.

Radiographs of the hands and feet were obtained

within four weeks of the first dose and at weeks 30 and 54 or upon premature withdrawal from the trial. For most patients, their MTX doses were able to be titrated to 20 mg/week and maintained through the endpoint evaluation (217 [72.8%] in the MTX–placebo group, 260 [69.7%] in the MTX–IFB 3 mg/kg group, and 254 [67.2%] in the MTX–IFB 6 mg/kg group).

Similar proportions of patients in the three treatment groups discontinued therapy, but more patients from the MTX–placebo group than both IFB–MTX groups withdrew because of a lack of efficacy from the medication. In contrast, there were more frequent withdrawals because of ADEs in the IFB–MTX group than in the MTX–placebo group.

Results

In this randomized, active-controlled trial, early treatment with combination therapy improved signs and symptoms of disease activity, inhibited radiographic progression of joint damage, and improved physical function better than MTX therapy alone.

The patients receiving MTX–IFB 3 mg/kg and MTX–IFB 6 mg/kg achieved significantly higher median ACR improvement results than those in the

TABLE 4 Radiographic Change from Baseline to Week 54 in the ASPIRE Trial

	IFB + MTX		
	Placebo + MTX (n = 282)	3 mg/kg q 8 weeks (n = 359)	6 mg/kg q 8 weeks (n = 363)
Total score			
Baseline			
Mean	11.3	11.6	11.2
Median	5.1	5.2	5.3
Change from baseline			
Mean	3.7	0.4*	0.5*
Median	0.4	0.0	0.0
Erosion score			
Baseline			
Mean	8.3	8.8	8.3
Median	3.0	3.8	3.8
Change from baseline			
Mean	3.0	0.3*	0.1*
Median	0.3	0.0	0.0
Joint space narrowing score			
Baseline			
Mean	3.0	2.9	2.9
Median	1.0	1.0	1.0
Change from baseline			
Mean	0.6	0.1*	0.2
Median	0.0	0.0	0.0

*P < .001 for each outcome against placebo.
From prescribing information for IFB.¹⁴

MTX–placebo patients (38.9%, 46.7 %, and 26.4%, respectively). There were no significant differences in clinical efficacy between the IFB 3 mg/kg and 6 mg/kg groups. ACR 20, ACR 50, and ACR 70 response rates were significantly higher in the MTX–3 mg/kg IFB and MTX–6 mg/kg IFB groups than in patients receiving MTX alone, while the ACR 90 response rate was significantly higher in the MTX–IFB 6-mg/kg group than in the MTX–placebo group.

More patients in the MTX–IFB 3-mg/kg and MTX–IFB 6-mg/kg groups (12.4% and 17.3%, respectively) sustained an ACR 70 response for at least six months, compared with the MTX–placebo patients (7.7%).

Radiographic progression of joint damage did not differ significantly between the IFB–MTX groups (Table 4). The separate analysis of the erosion and joint-space narrowing scores favored patients receiving the IFB–MTX therapies over those receiving MTX alone.

Patients treated with IFB–MTX demonstrated less progression of structural damage than patient receiving MTX alone, whether baseline acute-phase reactants (ESR and CRP) were normal or elevated. Of patients receiving IFB–MTX, 59% had no progression of structural damage compared to 45% of patients receiving MTX alone.

In a subset of patients who began the trial without erosions, IFB–MTX maintained an erosion-free state at one year in a greater proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively ($P < .01$). Fewer patients in the IFB–MTX groups (47%) developed erosions in uninvolved joints compared with those receiving MTX alone (59%).¹⁴

HAQ scores improved more in the MTX-3 mg/kg IFB and MTX-6 mg/kg IFB groups than in the group receiving MTX alone. The mean \pm SD and median interquartile range (IQR) decreases from baseline in HAQ scores from Weeks 30 to 54, averaged over time, were 0.80 ± 0.65 and 0.78 (0.38, 1.18) for the MTX–3 mg/kg IFB group and 0.88 ± 0.65 and 0.79 (0.48, 1.34) for the MTX–6 mg/kg IFB group, compared with 0.68 ± 0.63

and 0.75 (0.22, 1.04) for the MTX–placebo group (median decreases of 0.78 vs. 0.75 and 0.79 vs. 0.75; $P = .03$ and $P < .001$, respectively). From baseline to Week 54, more patients in the MTX-3 mg/kg IFB and MTX-6 mg/kg IFB groups improved their HAQ scores by at least 0.22 units (273/359 [76%] and 274/363 [75.5%], respectively) than those in the MTX–placebo group (184/282 [65.2%]) ($P < .003$ and $P = .004$, respectively). Of note, .22 is the minimum level of improvement considered to be clinically significant.

Improvement in the SF-36 physical component summary score also favored the combination of MTX-IFB over MTX therapy alone. From baseline to Week 54, the mean \pm SD and median (IQR) increases in the physical component summary score of the SF-36 were 11.7 ± 11.6 and 10.9 (2.6, 19.8) for the MTX–3 mg/kg IFB group and 13.2 ± 12.0 and 11.8 (4.4, 21.2) for the MTX–6 mg/kg IFB group, but only 10.1 ± 11.4 and 8.9 (1.4, 18.9) for the MTX–placebo group (median increases of 10.9 vs. 8.9 and 11.8 vs. 8.9; $P = .10$ and $P = .003$, respectively).

Safety Considerations

The safety profile of the IFB–MTX combination was similar to that observed in previous IFB trials except for an increased risk of serious infections in the IFB–MTX groups compared with those given MTX therapy alone. There was a higher incidence of pneumonia in patients receiving the IFB–MTX combinations (2%) than in those receiving MTX monotherapy (0%).

Four cases of tuberculosis (TB) were reported in the IFB treatments groups, consistent with previous reports indicating an increased risk for reactivation of latent TB with anti-TNF therapy. In addition, four cases of non-cutaneous malignancy were observed in this trial, all of which occurred in the 6-mg/kg IFB treatment group.

The incidence of nonlymphomatous malignancies, excluding non-melanoma skin cancers, was not significantly different in IFB-treated patients from clinical trials compared with the general population.

CROHN'S DISEASE

A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen: ACCENT I

*Hanauer et al., 2002*¹⁹

In mild cases, Crohn's disease (CD) can be treated with 5-aminosalicylates; however, many patients eventually need corticosteroids to control symptoms. Patients often become dependent on corticosteroids; approximately 45% of them are unable to discontinue corticosteroid therapy without exacerbation of their disease.

Purine antimetabolites and MTX are commonly prescribed for patients who are resistant to or dependent on corticosteroids, but these agents provide a remission rate of only 40% and have a slower onset of action.

Because TNF- α has a primary role in the pathogenesis of CD, IFB was evaluated as a potential therapy. When administered as a 5-mg/kg IV infusion, IFB induced remission in patients with moderate to severe CD and decreased the need for corticosteroids.

Trial Endpoints

The primary objective in ACCENT I was the efficacy and safety of repeated infusions of IFB in patients who improved after the initial infusion. The secondary objectives included the assessment of IFB's corticosteroid-sparing effects and safety in a large number of patients. The co-primary endpoints included time to loss of response and remission at Week 30.

This multicenter, randomized, double-blinded trial monitored patients for up to 54 weeks.

Methods

Patients were eligible for inclusion in the trial if they:

- had CD for at least three months.
- had a Crohn's Disease Activity Index (CDAI) score between 220 and 400.
- received treatments with the following agents:
 - 5-aminosalicylates or antibiotics (if the dose remained constant for four weeks before the screening visit)
 - corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 40 mg/day of prednisone or less (with the dose remaining stable for three weeks)
 - azathioprine and 6-mercaptopurine (with the dose stable for eight weeks)
 - MTX (with a stable dose for six weeks)

Individuals not receiving medicinal therapy had to have treatment discontinued for at least four weeks before

screening.

Patients were excluded from the trial if they had received previous treatment with IFB or any other medication with activity against TNF- α .

At Week 0, all patients received a 5-mg/kg infusion of IFB. Two weeks later, the patients were evaluated for their response to therapy. If the patients achieved a decrease in their CDAI score of 70 points or more from the baseline and at least a 25% reduction in the total score, they were randomly assigned to receive subsequent infusions at the second and sixth weeks and every eight weeks for 46 weeks. The patients were assigned as follows:

- group 1 (placebo)
- group 2 (IFB 5 mg/kg)
- group 3 (IFB 5 mg/kg at the second and sixth weeks, followed by 10 mg/kg thereafter)

At Week 14 or later, patients who had initially responded but then worsened were eligible to cross over to active episodic re-treatment. This regimen comprised 5, 10, or 15 mg/kg IFB from that point forward on an as-needed basis, for patients originally assigned to groups 1, 2, and 3, respectively. Worsening was defined by (1) an increase in the CDAI of at least 70 points from the qualifying score of at least 175, (2) an increase in the CDAI of 35% or more from the baseline value, or (3) the introduction of a new treatment for active CD. Patients and physicians remained unaware of the treatment assignment. All data obtained after episodic re-treatment were included in the safety analyses but not in the efficacy analyses.

Patients receiving corticosteroids were to maintain a stable dose until Week 6, after which a defined tapering schedule was started if the patient's condition had improved. Patients who entered the trial receiving corticosteroid doses of more than 20 mg/day prednisone equivalent had their treatment tapered at a maximum rate of 5 mg/week; the maximum rate for patients receiving 20 mg/day prednisone equivalent or less was 2.5 mg/week. Aminosaliclates and immunomodulators were maintained at a constant dose.

Patients were assessed at Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, and 54. At each visit, the primary investigators or site coordinators evaluated ADEs by directly questioning the patients. Samples for clinical laboratory assessments as well as patients' CDAI scores were also obtained. The Inflammatory-Bowel Disease Questionnaire (IBDQ) was used primarily to assess patients' health-related quality of life.

Blood samples for measuring IFB concentrations were collected immediately before each infusion and at the end (at Weeks 0, 22, and 46). Serum samples were collected to determine the presence of ANAs and or anti-dsDNA antibodies.

Results

Of the 580 patients enrolled, 573 patients were started on therapy with IFB 5 mg/kg, and 335 patients (58%) were responders at Week 2. Baseline characteristics of these responders, compared with those of the nonresponders, were similar except for the duration of CD, previous segmented resection, and CRP concentrations. By Week 54, 124 patients (22%) had discontinued maintenance treatment.

The proportion of patients who discontinued treatment was similar in all groups: group 1 (38 patients, 20%), group 2 (49 patients, 26%), and group 3 (37 patients, 19%). In group 1, the most common reason for withdrawal was a lack of efficacy (23 patients, 12%). In groups 2 and 3, the most common reasons were ADEs (38 patients, 10%) and a lack of efficacy (31 patients, 8%).

Throughout follow-up, patients who continued active treatment showed a greater therapeutic benefit than patients who were re-treated with placebo. At Week 30, the proportion of responders in remission at Week 2, was higher in group 2 (44 patients, 39%) and in group 3 (50 patients, 45%) than in group 1 (23 patients, 21%). At Week 54, the results were similar.

There were no differences in the rate of remission between groups 2 and 3 at Week 30 or at Week 54. Patients in groups 2 and 3 had a significantly longer time to loss of response than patients in group 1 ($P = .0002$). The median time to loss of response was 46 weeks (IQR, 17 to greater than 54) in groups 2 and 3 combined, compared with 19 weeks (range, 10–45) in group 1. When compared separately, patients in both groups 2 and 3 had a significantly longer time to loss of response than patients in group 1. At Week 54, when combined, three times as many patients (32 patients, 29% versus five patients, 9%) in groups 2 and 3 discontinued corticosteroids use while in clinical remission when compared with patients in group 1.

The median corticosteroid dose was reduced more rapidly in groups 2 and 3 (0 mg/day by Week 22) than in group 1 (10 mg/day at Week 22).

Median CDAI scores were at or near remission at Week 2. The proportion of patients who maintained a clinical remission at every visit from Week 14 to Week 54 was 11% for group 1, 25% for group 2, and 33% for group 3.

At Weeks 30 and 54, significant improvement from baseline was seen among the 5-mg/kg and 10-mg/kg IFB-treated groups, compared with the placebo group in the disease-specific IBDQ, particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality-of-life questionnaire, SF-36.¹⁴

Safety Considerations

Safety data for all 573 treated patients were reported

according to the actual treatment received. Headache, abdominal pain, and upper respiratory tract infections were reported most frequently.

Infusion reactions, generally characterized by headache, dizziness, nausea, injection-site irritation, flushing, chest pain, dyspnea, and pruritus, occurred in 61 of 993 (6%) and 45 of 1,033 (4%) group 2 and 3 IFB infusions, respectively, compared with 23 of 837 (3%) of group 1 infusions. Infusion reactions led to discontinuation of IFB in 12 patients (nine in group 2, three in group 3). Among the 442 patients with evaluable samples, 42 of 254 infusions (16%) resulted in infusion reactions among patients positive for antibodies to IFB, compared with 55 of 656 (8%) and 47 of 1,470 (3%) in patients negative for antibodies to IFB and with inconclusive status, respectively.

Over the course of the trial, the lowest incidence of infusion reactions occurred among patients receiving both steroids and immunosuppressive agents (7/85 [8%]) compared with 17/84 of patients (20%) receiving only immunosuppressives, 47/207 of patients (23%) receiving steroids alone, and 62/197 of patients (32%) without corticosteroids or immunosuppressives. Serum-sickness-like reactions were seen in three patients (2%) in group 1, five patients (3%) in group 2, and six patients (3%) in group 3. Reactions were generally seen after one to five maintenance infusions.

By Week 54, infusion syndrome (five patients), allergic reaction (four patients), arthralgia (four patients), serum sickness (four patients), and rash (three patients) were the most common ADEs leading to discontinuation of IFB.

Serious infections occurred in 22 (4%) of 573 patients. By Week 14, there was no difference in the incidence of infections requiring treatment between patients receiving a single IFB infusion (25 of 188 patients [13%]) and those receiving multiple infusions (51 of 385 patients [13%]).

At Week 54, 186 patients (32%) had an infection requiring treatment. A 35-year-old woman died of sepsis secondary to a small bowel obstruction two months after the Week 6 IFB infusion (group 2). Two additional patients died before the end of the trial: a patient in group 2 died of myocardial infarction 25 days after the last infusion, and a patient in group 2 died of sepsis 144 days after the last trial infusion. For both of these patients, the events leading to death were judged to be probably not related to the trial agent.

A 64-year-old woman developed TB four weeks after her Week 14 infusion and was successfully treated. This patient received IFB 5 mg/kg at Weeks 0, 2, and 6, followed by a crossover to episodic re-treatment because of disease flare, and IFB 15 mg/kg at Week 14.

Six patients (1%) had a malignant disorder: an epithelial-cell skin neoplasm was diagnosed about 6.5 months after the IFB infusion (group 1); a natural-

killer-cell lymphoma was diagnosed about 10 months after the Week 14 infusion (group 1, patient discontinued treatment 50 days after the Week 14 infusion); a basal-cell carcinoma was identified two weeks after receipt of the Week 6 infusion (group 2); a hypernephroma for which the patient underwent surgery was diagnosed nine weeks after the Week 6 infusion (group 2); a malignant breast neoplasm was recognized 51 days after the Week 30 infusion (group 2); and a bladder carcinoma was seen 49 days after the Week 42 infusion (group 3).

More group 2 and 3 patients developed anti-dsDNA antibodies and ANAs (123 [34%] and 363 [56%], respectively) than group 1 patients (19 [11%] and 63 [35%], respectively). One patient (group 3) developed arthralgia in conjunction with positivity for ANAs and anti-dsDNA antibodies, which the investigator judged to be a lupus-like syndrome. There was no evidence of renal or other organ involvement. This patient responded to discontinuation of IFB and administration of prednisone. Another patient (group 3) was judged to have a lupus-like syndrome caused by positivity for anti-histone antibodies. This patient discontinued the trial at Week 30 because of noncompliance.

A Crohn's Disease Clinical Study Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn's Disease: ACCENT II

*Sands et al., 2004*²⁰

ACCENT II was a multicenter, double-blinded, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of IFB therapy in maintaining closure of draining fistulas among patients who responded to a three-dose induction regimen of IFB.

Three hundred six adult patients with CD and with one or more draining abdominal or perianal fistulas for at least three months were screened. Setons were permitted at screening but were required to be removed by the second week of the trial. Concurrent therapies for CD were permitted, but patients were excluded from the trial if they had a stricture or abscess for which they might need surgery or if they had previously been treated with IFB. The doses of all concomitantly taken medications remained constant, except for corticosteroids, which were tapered.

Trial Endpoint

The *primary analysis* was the time to the loss of response among patients who responded initially at Week 14 and who underwent randomization.

Loss of response was defined by the recurrence of draining fistulas, the need for a change in medication for CD or the need for additional therapy from persis-

tent or worsening luminal disease activity, the need for surgical procedure, or discontinuation of the trial medication because of a perceived lack of efficacy.

A *complete response* was defined as the absence of draining fistulas.

A *response* was defined as a reduction of at least 50% from baseline in the number of draining fistulas at consecutive visits four or more weeks apart. A patient was classified as having a response if a response was observed at both Weeks 10 and 14.

Methods

Patients received an initial 5-mg/kg IV infusion of IFB at Weeks 0, 2, and 6. Responders, patients with a reduction of at least 50% from baseline in the number of draining fistulas at consecutive visits four or more weeks apart, were randomly assigned to receive an infusion of either placebo or 5 mg/kg of IFB at Weeks 14, 22, 30, 38, and 46. These patients were closely observed until Week 54.

Patients were assessed at Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, and 54. Fistula examinations were conducted at each visit, and the CDAI score was used to determine disease activity.

The IBDQ was administered to assess the health-related quality of life. Beginning at Week 22, patients receiving placebo with a loss of response were eligible to cross over to treatment with IFB 5 mg/kg. Patients in the IFB maintenance groups could switch to treatment with 10 mg/kg; all crossovers were masked.

Results

Of the 306 patients enrolled, 282 were available for randomization. Of these patients, 195 were in response at Week 14. The onset of response was rapid, with an increase in response rate after each of the three induction infusions.

Patients who had a response at the time of randomization and who received IFB maintenance therapy had a significantly longer time to loss of response than those who received placebo ($P < .001$). After randomization, the median time to the loss of response was 14 weeks with placebo and more than 40 weeks with IFB.

In both groups of patients, the most common cause of loss of response was the need for a change in treatment (38% with placebo and 25% with IFB), followed by the recurrence of fistulas (22% and 16%, respectively).

At Week 54, 23% of patients in the placebo maintenance group still had a response (23 of 98), compared with 46% of patients in the IFB maintenance group (42 of 91, $P = .001$). In a multivariate regression model, no baseline characteristics were independent predictors of a sustained response at Week 54.

At Week 54, 19% of patients in the placebo maintenance group had a complete response (19 of 98), compared with 36% of patients in the IFB maintenance

TABLE 5 ACCENT II: Summary of Week 54 Safety Analysis for All Randomized Patients

Variable	Placebo Maintenance (n = 144)	IFB Maintenance (n = 138)	Total (n = 282)	P Value*
Extent of IFB exposures (54 weeks)	4.3 ± 1.7	7.5 ± 1.3	5.9 ± 2.2	<.001
Total dose (mg/kg)	21.4 ± 8.3	41.1 ± 10.9	31.1 ± 13.8	<.001
Adverse events leading to discontinuation of the study agent				
No. of patients (%)	12 (8)	5(4)	17(6)	.1
Serious adverse events				
No. of patients (%)				
All events	33 (23)	19 (14)	52 (18)	.05
Reasonably related events†	9 (6)	3 (2)	12 (4)	.09
Infections				
No. of patients (%)				
Infections requiring antimicrobial therapy ‡	39 (27)	47 (34)	86 (30)	.20
Serious infections	9 (6)	4 (3)	13 (5)	.18
New fistula-related abscesses				
No. of patients (%)	25 (17)	17 (12)	42 (15)	.25
Infusion reactions				
No. of patients (%)	24 (17)	22 (16)	46 (16)	
During induction	11 (8)	9 (7)	20 (7)	
During maintenance	4 (3)	13 (9)	NA	.02
During therapy after crossover	14 (23)	3 (9)	17 (18)	

Plus-minus values are means plus or minus the standard deviation.

* P values are for the comparison between the placebo maintenance and IFB maintenance groups.

† Events deemed by the investigator to be possibly, probably, or definitely related to the study agent (or that had an unknown relation) were recorded as “reasonably related.”

‡ The analysis does not include one patient who was found to have a positive skin test with purified protein derivative before the infusion at 30 weeks. Isoniazid was initiated, and the patient subsequently received all remaining study infusions.

From Sands BE, Anderson FH, Bernstein CN, et al. *N Engl Med J* 2004;350:883. © Massachusetts Medical Society.²⁰

group (33 of 91, *P* = .009).

The median increases from baseline in scores for the IBDQ at Weeks 30 and 54 were 4 and 5, respectively, in the placebo maintenance group and 14 and 10, respectively, in the IFB maintenance group (*P* = .002 and *P* = .03 for the comparisons between groups at Weeks 30 and 54, respectively).

Among randomized patients with a response during maintenance therapy who subsequently lost their response because of a recrudescence of draining fistulas, 61% of patients (25 of 41) who crossed over from placebo maintenance to IFB (5 mg/kg) maintenance reestablished a response. Similarly, 57% of patients (12 of 21) re-established a response on crossing over from an IFB dose of 5 mg/kg to a dose of 10 mg/kg.

Safety Considerations

ADEs occurred in 92% of patients taking placebo and in 89% of patients taking IFB. Only a few patients discontinued therapy because of ADEs (8% and 4%, respectively). The most frequently reported ADEs in both groups were similar in nature and incidence to those described elsewhere in patients with CD. Slightly more patients in the placebo group reported a new fistula-related abscess (Table 5).

The most frequently reported serious ADEs were related to the gastrointestinal (GI) system. Worsening of CD was the most common individual serious ADE, occurring in 6% of all randomized patients. No deaths or cancers occurred during the trial; however, two deaths have been reported during the long-term follow-up.

One patient (a 78-year-old woman) died of sepsis

related to advanced CD approximately nine months after her last (fourth) trial infusion of IFB. She also received an infusion of IFB seven months before her death. The other patient (a 52-year-old man) died of multisystem organ failure (heart failure, pneumonia, renal failure, and amyloidosis) 18 months after receiving the three-dose induction regimen of IFB. This patient did not receive any additional IFB.

Two cases of cancer have also been reported during long-term follow-up. One patient (a 42-year-old man with a 20-year history of colonic CD) received a diagnosis of rectal carcinoma approximately two years after his last IFB infusion.

The second patient (a 36-year-old man with a 22-year history of ileal CD and perianal fistula). He received a diagnosis of rectal adenocarcinoma approximately 19 months after his last (sixth) IFB infusion.

Multiple sclerosis developed in one patient who was assigned to placebo maintenance, approximately one month after an IFB infusion that was not related to the trial. Infections requiring antimicrobial treatment occurred in nearly one third of patients. Five percent of all randomized patients had a serious infection. The only serious infection reported in more than two patients was abscess. Opportunistic infections included one case of cytomegalovirus infection reported 39 days after the third induction infusion and one case of cutaneous *Nocardia* infection reported eight days after the first induction infusion.

The proportion of infusions accompanied by an infusion reaction was low. Infusion reactions occurred more frequently in association with IFB infusions (70 of 1,728 infusions [4%]) than with placebo infusions (four of 419 infusions [1%], $P < .001$). In general, the reactions were not severe enough to warrant the discontinuation of treatment, and only one infusion reaction met the definition of a serious ADE.

Patients assigned to IFB maintenance therapy were more than twice as likely to have ANAs and nearly four times as likely to have antibodies against dsDNA than patients assigned to placebo maintenance. A lupus-like syndrome developed in one patient; however, the results of tests for ANAs and antibodies against dsDNA were negative in this patient.

ACTIVE CROHN'S DISEASE IN PEDIATRIC PATIENTS¹⁴

Study Peds Crohn's

The safety and efficacy of IFB were assessed in a randomized, open-label study (Study Peds Crohn's) in 112 pediatric patients six to 17 years old with moderately to severely active Crohn's disease (CD) and an inadequate response to conventional therapies. The median age was 13 years, and the median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 (on a scale of 0 to 100). All patients were required to be on a stable dose of 6-mercaptopurine, azathioprine, or methotrexate; 35% were also receiving corticosteroids at baseline.

All patients received induction dosing of 5 mg/kg IFB at Weeks 0, 2, and 6. At Week 10, 103 patients were randomly selected to receive a maintenance regimen of 5 mg/kg IFB given either every eight weeks or every 12 weeks.

At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥ 15 points and total PCDAI score of ≤ 30 points), and 59% were in clinical remission (defined as PCDAI score of ≤ 10 points).

The proportion of pediatric patients achieving clinical response at Week 10 compared favorably with the proportion of adults achieving a clinical response in ACCENT I. The study definition of clinical response in Study Peds Crohn's was based on the PCDAI score, whereas the CDAI score was used in ACCENT I.

At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the every-eight-week treatment group than in the every-12-week treatment group (73% vs. 47% at Week 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in clinical remission was also greater in the every-eight-week treatment group than in the every-12-week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54) (see Table 9 on page 33).

For patients in Study Peds Crohn's receiving corticosteroids at baseline, the proportion of patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the every-eight-week maintenance group and 33% for the every-12-week maintenance group.

At Week 54, the proportion of patients able to discontinue corticosteroids while in remission was 46% for the every-eight-week maintenance group and 17% for the every-12-week maintenance group.

ANKYLOSING SPONDYLITIS

Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy: ASSERT

*van der Heijde et al.*²¹

ASSERT, a multicenter, randomized, placebo-controlled, double-blinded trial, was designed to evaluate the efficacy and safety of IFB in patients with ankylosing spondylitis (AS).

Adult patients classified as having AS (according to the modified New York criteria) for at least three months prior to screening, with a Bath AS Disease Activity Index (BASDAI) score of 4 or higher (range, 0–10), and with a spinal pain assessment score of 4 or higher on a visual analogue scale (VAS) (range, 0–10 cm) were eligible for the trial. Patients were excluded from the trial if they had a history of total ankylosis of the spine or any other inflammatory rheumatic disease; fibromyalgia; a serious infection within two months prior to randomization; tuberculosis (active or latent) or recent contact with active-tuberculosis patients; or an opportunistic infection within six months of screening.

Patients were allowed to receive concurrent stable doses of NSAIDs, acetaminophen, or tramadol, but they were not permitted to receive sulfasalazine or

MTX within two weeks prior to screening.

Patients were not permitted to use systemic corticosteroids within one month before screening; anti-TNF therapy other than IFB within three months before screening; IFB at any time prior to screening; DMARDs other than sulfasalazine or MTX within six months before screening; or cytotoxic drugs 12 months before screening.

Trial Endpoint and Methods

The patients were randomly assigned, in a 3:8 ratio, to receive infusions of placebo or IFB 5 mg/kg at Weeks 0, 2, 6, 12, and 18. The primary endpoint was the proportion of patients with a 20% improvement response according to the criteria of the Assessment in Ankylosing Spondylitis (ASAS) at Week 24.

An ASAS 20 responder was defined as a patient who showed at least 20% improvement from baseline of at least one unit in at least three of four assessment criteria:

- global assessment
- spinal pain
- functioning according to the Bath Ankylosing Spondylitis Functional Index (BASFI)
- morning stiffness

TABLE 6 Incidence of Adverse Drug Events from Infliximab Through Week 24 of the ASSERT Trial*

	Placebo (n = 75)	IFB 5 mg/kg (n = 202)
Patients with an adverse event	54 (72.0)	166 (82.2)
Patients with any serious adverse event	2 (2.7)	7 (3.5)
Patients with any infusion reaction	7 (9.3)	22 (10.9)
Patients with any infection	27 (36.0)	86 (42.6)
Patients with any serious infection	0 (0.0)	2 (1.0)
Adverse events occurring in ≥5% of patients in either treatment group		
Upper respiratory tract infections	11 (14.7)	28 (13.9)
Pharyngitis	2 (2.7)	21 (10.4)
ALT level increased	3 (4.0)	19 (9.4)
Headache	6 (8.0)	18 (8.9)
Rhinitis	2 (2.7)	15 (7.4)
Diarrhea	4 (5.3)	11 (5.4)
Pain	4 (5.3)	11 (5.4)
AST level increased	2 (2.7)	11 (5.4)
Arthritis	4 (5.3)	6 (3.0)
Rash	4 (5.3)	5 (2.5)

* Values are the number (%) of patients.

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

From van der Heijde D, Dijkmans B, Geusens P, et al. *Arthritis Rheum* 2005;52(2):588. © American College of Rheumatology. Reproduced with permission of John Wiley & Sons, Inc.²¹

Furthermore, ASAS 20 responders must not have experienced any deterioration from baseline values.

Several tools were used to measure overall functions:

- The BASDAI was used to evaluate disease activity (i.e., fatigue, spinal pain, joint pain, and morning stiffness), night pain VAS scores, the patient's global assessment, and the CRP level.
- The Bath Ankylosing Spondylitis Metrology Index (BASMI) was used to measure physical function and range of motion and chest expansion. Eight questions related to the patient's functioning, and two questions related to patients' ability to cope with everyday life.
- Other musculoskeletal assessments included the Total Swollen Joint Index and the Enthesis Index, which measured the degree of tenderness.
- The SF-36 was used to assess quality of life.

At Week 24, serum samples were assessed at baseline for the presence of ANAs to IFB. All statistical tests were two-sided and were performed at $P = .05$, with no statistical adjustments for multiple comparisons.

Overall, 279 patients were randomly assigned to treatment with placebo ($n = 78$) or IFB ($n = 201$). The trial population consisted of mostly men (80.6%) whose median age was 40.0 years. The median duration of AS was 8.8 years.

Results

More men received placebo (87.2%) than IFB (78.1%). Most of the patients in both treatment groups completed the 24-week trial period. After 24 weeks, 123 patients (61%) in the IFB group were ASAS 20 responders, compared with 15 patients (19.2%) in the placebo group ($P < .001$). As early as Week 2, a difference between the two groups was observed and was maintained over the 24-week observation period.

In patients with baseline CRP levels three times or less than the upper limit of normal (ULN), 46.3% of IFB-treated patients achieved an ASAS 20 response, compared with 21.1% of placebo-treated patients. For patients with baseline CRP levels more than three times the ULN, 74.5% of IFB-treated patients achieved an ASAS 20 response, compared with 17.5% of 40 placebo-treated patients ($P < .001$). Significantly more patients in the IFB group were ASAS 20 responders over the total 24 weeks.

At Week 24, 93 patients in the IFB group (47.0%)

and nine patients in the placebo group (12.0%) were ASAS 40 responders ($P < .001$). Also, 97 patients in the IFB group (49%) achieved a 20% improvement in five of six ASAS assessment domains, compared with six patients in the placebo group (8.0%) ($P < .001$). At this point, 45 patients in the IFB group (22.4%) achieved ASAS partial remission, compared with only one patient in the placebo group (1.3%) ($P < .001$).

Measurements of disease activity (from the BASDAI score, night pain, patients' global assessment, and CRP levels) and physical functions (BASFI score) were significantly improved in the IFB group, compared with the placebo group. Significantly more patients in the IFB group had at least a 50% improvement in their BASDAI scores from baseline to Week 24.

Ninety-four patients (47.5%) in the IFB group improved their BASFI score by 2 points or greater, compared with 10 patients (13.3%) in the placebo group ($P < .001$).

Patients receiving IFB also demonstrated a statistically significant improvement in range of motion. The median improvement from baseline in BASMI scores was 1.0 in the IFB group and 0.0 in the placebo group ($P = .019$). Patients in the IFB group had significantly greater improvement in all components of the BASMI except for lumbar flexion.

Although no significant change was observed in the Mander Enthesis Index scores ($P = .800$), there was a significant improvement from baseline at Week 24 in the enthesitis component of the BASDAI for patients in the IFB group (a median improvement of 2.9, compared with a median worsening of 0.2 in the placebo group; $P < .001$), as well as significant improvement in their median Swollen Joint Index score ($P = .019$).

At Week 24, patients in the IFB group showed a significant improvement from baseline in the physical component summary score of the SF-36 compared with patients in the placebo group (median change from baseline, 10.2 vs. 0.8, respectively; $P < .001$).

Safety Considerations

A higher proportion of patients receiving IFB (82.2%) experienced one or more ADEs, compared with patients receiving placebo (Table 6). Most ADEs were mild or moderate in severity, occurring at comparable or lower rates in the IFB patients. Frequently observed side effects in the IFB group included upper respiratory infections, pharyngitis, elevated liver enzyme levels, headache, and rhinitis.

PSORIATIC ARTHRITIS^{6,14,22}

Induction and Maintenance Psoriatic Arthritis Clinical Trial: IMPACT 2

Antoni et al.

IMPACT 2 was a phase 3 double-blind, placebo-controlled, randomized, parallel-group 54-week trial that further evaluated the efficacy of infliximab (IFB) in patients with active psoriatic arthritis.

Trial Endpoints

The primary efficacy endpoint was the proportion of patients achieving a 20% improvement in the ACR criteria (ACR 20) at Week 14. The ACR 20 was assessed at Weeks 2, 6, 14, and 24. Individuals with missing ACR 20 and Psoriatic Arthritis Response Criteria (PsARC) data at Weeks 14 and 24 were considered non-responders.

Secondary efficacy responses were evaluated at most visits from screening through Week 24; these included the PsARC, the Psoriasis Area and Severity Index (PASI), dactylitis and enthesopathy assessments, and the SF-36 questionnaire. Efficacy and safety were assessed at 54 weeks.

Methods

The investigators enrolled 200 patients with active PsA for six months or more who had an inadequate response to DMARDs or NSAIDs. Subjects had active articular disease (five or more swollen and tender joints each), a psoriatic target skin lesion (2 cm or more in diameter), and at least one of the following: serum CRP of 1.5 mg/dl or more, or morning stiffness lasting 45 minutes or more.

Patients were excluded from the trial if they had evidence of latent or active tuberculosis (TB) or chronic or clinically significant infection, malignancy, or congestive heart failure or if they had ever used TNF- α inhibitors. Concomitant MTX treatment (up to 25 mg/week) was allowed for at least three months before the first infusion and was maintained at a stable dose for at least four weeks prior to the first infusion. Oral corticosteroids were permitted at a stable dose equivalent to no more than prednisone 10 mg/day.

Stable MTX doses of 25 mg/week or less at trial entry and stable oral corticosteroid doses equivalent to 10 mg/day or less of prednisone were permitted; DMARDs and topical systemic medications for psoriasis (except low-potency topical corticosteroids for the face and groin) were prohibited. The use of DMARDs (other than MTX) or intra-articular corticosteroids was also prohibited within four weeks before the first infusion.

IFB 5 mg/kg (n = 100) or placebo (n = 100) was infused at Weeks 0, 2, 6, 14, and 22; patients with

inadequate response (less than 10% improvement in swollen or tender joint counts) entered “early escape” and received IFB 5 mg/kg at Weeks 16, 18, and 22. At Week 24, all placebo-treated patients crossed over to IFB induction. Dosing continued for all patients through Week 46.

The severity of psoriasis at baseline was defined on the basis of body surface area (BSA) involvement as follows: mild (less than 5%), moderate (5% to less than 10%), and severe (at least 10%).

In patients with at least 3% BSA psoriasis involvement at baseline, the Psoriasis Area and Severity Index (PASI) was used to assess psoriasis activity at baseline and at Weeks 2, 6, 14, and 24. PASI is a composite score, ranging from 0 to 72, that is used for assessing and grading the severity of psoriatic lesions and their response to treatment. PASI includes assessments of the extent of skin involvement, erythema, plaque thickness, and the degree of scaling.⁶ In addition, the target lesion score (erythema, plaque induration, and scaling rated on a scale of 0–4 each) was assessed at Weeks 0, 14, and 24 in all patients, irrespective of their baseline PASI scores.

Safety evaluations that included the monitoring of ADEs and routine laboratory tests were performed at every visit through the 24th week.

Of the 320 patients screened, 200 were enrolled; of these, 185 (93%) completed the trial through Week 24. The placebo and IFB groups were generally well balanced with regard to demographics and baseline disease characteristics. A substantial proportion of patients had dactylitis, enthesopathy, or both. Most of the patients (170 of 200, or 85%) had BSA psoriasis involvement of at least 3%, and more than 70% had moderate or severe psoriasis.

Similar proportions of individuals received MTX at baseline (45% and 47% in the placebo and IFB groups, respectively) at a mean dose of 15 mg/week in the placebo group and 16 mg/week in the IFB group.

Results

A significantly higher proportion of IFB-treated individuals ($P < .001$) achieved ACR 20 responses at Week 14 (58%) and at Week 24 (54%), compared with those receiving placebo (11% and 16% at Weeks 14 and 24, respectively). At Week 14, 36% of the IFB patients achieved an ACR 50 response, and 15% achieved an ACR 70 response, compared with 3% and 1%, respectively, of individuals receiving placebo ($P < .001$).

The number of ACR 50 and ACR 70 responses increased from Week 14 to Week 24, at which time 41% of IFB patients achieved an ACR 50 response and 27% achieved an ACR 70 response, compared with 4% and 2% of the placebo-treated patients ($P < .001$).

At Week 14, the percentage of patients who achieved

an ACR 20 response was not significantly higher among the MTX users (60%) than the MTX non-users (57%), and fewer MTX users than MTX non-users achieved an ACR 50 response (28% vs. 43%) and an ACR 70 response (9% vs. 21%).

However, 77% of IFB-treated patients and 27% of placebo-treated individuals had improved at Week 14, according to PsARC ($P < .001$). At Week 24, similar findings in improvement were observed (70% with IFB, 32% with placebo; $P < .001$).

Among the 170 individuals who had BSA psoriasis involvement of at least 3% at baseline, more IFB-treated patients experienced at least 50%, 75%, and 90% improvement in PASI (PASI 75) scores from baseline to Week 14, compared with placebo-treated patients ($P < .001$). The proportion of patients with at least a 75% improvement in PASI was significantly greater with IFB than with placebo at Week 14 (64% vs. 2%; $P < .001$) and Week 24 (60% vs. 1%; $P < .001$).

At Week 54, 59% had achieved ACR 20 and 50% maintained PASI 75 in the IFB treatment group. These responses were irrespective of MTX use.²²

The skin response to IFB therapy was evident as early as the second week and was maintained through the 24th week. Patients treated with IFB also experienced a significant ($P < .001$) improvement from baseline to Week 14 in the target lesion score relative to placebo-treated patients (65.6% vs. -0.3%; $P < .001$), with responses maintained through Week 24.

The physical and mental components of the SF-36 summary scores were significantly improved from baseline to Week 14 in the IFB group of patients ($P < .001$), compared with the placebo group. At Week 24, results were also similar for the physical ($P = .001$) and mental ($P = .047$) components.

Compared with placebo, treatment with IFB resulted in improvements in the components of the ACR response criteria as well as in dactylitis and enthesopathy.

Although similar numbers of patients treated with IFB and placebo (41% and 40%, respectively) had dactylitis of one or more digits at baseline, fewer IFB-treated patients had digits with dactylitis, compared with patients receiving placebo at Week 14 (18% vs. 30%; $P = .025$) and at Week 24 (12% vs. 34%; $P < .001$).⁶

In addition, although 42% and 35% of patients in the IFB and placebo groups, respectively, had enthesopathy at baseline, a significantly lower proportion of patients who received IFB had enthesopathy, compared with patients treated with placebo at both Week 14 (22% vs. 34%; $P = 0.016$) and at Week 24 (20% vs. 37%; $P = .002$).⁶ The clinical response was maintained through Week 54.

Radiographic Response¹⁴

Structural damage in both the hands and the feet was assessed radiographically by the change from baseline in the van der Heijde–Sharp (vdH-S) score, modified by the addition of hand distal interphalangeal (DIP) joints. The total modified vdH-S score is a composite score of structural damage that measures the number and size of joint erosions and the degree of joint-space narrowing (JSN) in the hands and feet.

At Week 24, IFB-treated patients had less radiographic progression than placebo-treated patients (mean change of -0.70 vs. 0.82, $P < .001$). IFB-treated patients also had less progression in their erosion scores (-0.56 vs. 0.51) and JSN scores (-0.14 vs. 0.31). Patients in the IFB group demonstrated continued inhibition of structural damage at Week 54. Most patients showed little or no change in the vdH-S score during this 12-month study (median change of 0 in both patients who initially received IFB or placebo).

More patients in the placebo group (12%) had readily apparent radiographic progression, compared with the IFB group (3%).

Safety Considerations

IFB was generally well tolerated. The most common ADEs through Week 24 in IMPACT 2 are shown in Table 7.

The incidence of serious ADEs, infections, and infusion reactions was similar between the treatment groups. The percentage of individuals who experienced ADEs leading to withdrawal from the trial in the combined IFB group was higher than that in the placebo group (4% vs. 1%).

Few clinically significant abnormal laboratory findings were reported. Aminotransferase elevations occurred more frequently in IFB-treated patients compared with placebo-treated patients. Most of these elevations were less than three times the ULN. Markedly abnormal alanine transaminase (ALT) and/or aspartate transaminase (AST) values (predefined as ≥ 150 IU/L and $\geq 100\%$ increase from baseline) were reported in a total of five patients in the combined IFB group compared to no patients in the placebo group. All five patients discontinued trial infusions. One patient was lost to follow-up, but ALT/AST levels returned to normal or less than 1.5 times the ULN in all four patients for whom follow-up data were available. None of these elevations was associated with signs of liver failure. One of the five patients was receiving concomitant MTX.

Through Week 24, no deaths occurred, and no opportunistic infections (including tuberculosis), congestive heart failure, demyelinating or new autoimmune disorders, serious infusion reactions, anaphylaxis, or delayed hypersensitivity reactions were reported.

TABLE 7 Most Common Adverse Events ($\geq 5\%$) in IMPACT 2 at Week 24 for Treated Patients

Adverse Events through (Week 24 for Treated Patients)	IFB Combined* (n = 150)	Placebo (n = 97)
≥ 1 adverse event	100 (66.7%)	65 (67.0%)
Upper respiratory tract infection	15 (10.0%)	14 (14.4%)
Headache	9 (6.0%)	5 (5.2%)
Increased alanine aminotransferase (≥ 3 times ULN)	9 (6.0%)	1 (1.0%)
Pharyngitis	8 (5.3%)	4 (4.1%)
Sinusitis	8 (5.3%)	4 (4.1%)
Dizziness	6 (4.0%)	5 (5.2%)
Adverse events leading to withdrawal	6 (4.0%)	1 (1.0%)
Serious adverse events	13 (8.7%)	6 (6.2%)
Infusion reactions	11 (7.3%)	6 (6.2%)

* The combined group receiving IFB included all patients who received IFB, all placebo patients who switched to IFB at Week 16, and all patients who incorrectly received IFB.

IMPACT = Induction and Maintenance Psoriatic Arthritis Clinical Trial; ULN = upper limit of normal.
Data from Antoni.⁶

One placebo-treated patient developed a basal cell carcinoma of the skin. A small percentage (4.5%) of patients in the combined IFB group were positive for antibodies to IFB through Week 22. Newly positive ANAs (defined by titer $\geq 1:160$) were detected in 9.9% of patients in the combined IFB group compared with

2.6% of patients in the placebo group. Newly positive anti-dsDNA antibodies were detected in three ANA-positive patients treated with IFB and no ANA-positive patients treated with placebo. None of the patients developed a lupus-like condition.

ULCERATIVE COLITIS^{13,14}

Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2)

The safety and efficacy of IFB were assessed in two multicenter, randomized, double-blind, placebo-controlled clinical trials (ACT 1 and ACT 2) in 728 patients with moderately to severely active ulcerative colitis (UC) (Mayo score 6 to 12 [of possible range 0–12], Endoscopy subscore >2) with an inadequate response to conventional oral therapies.¹⁴

Trial Endpoints¹³

The primary endpoint was a clinical response at Week 8. Secondary endpoints included a clinical response or clinical remission with discontinuation of corticosteroids at Week 30 in both ACT 1 and ACT 2 and at week 54 in ACT 1; a clinical remission and mucosal healing at weeks 8 and 30 in both studies and at week 54 in ACT 1; and a clinical response at Week 8 in patients with a history of disease that was refractory to corticosteroids.

Clinical response was defined as a decrease from baseline in the total Mayo score of at least three points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least one point or an absolute subscore for rectal bleeding of zero (0) or 1.

Clinical remission was defined as a total Mayo score of two points or lower, with no individual subscore exceeding one point.

Mucosal healing was defined as an absolute subscore for endoscopy of 0 or 1.

Methods¹³

All eligible patients had an established diagnosis of UC. Patients with positive tuberculin skin tests with the use of purified protein derivative (PPD) were ineligible for enrollment. Standard chest radiographs were also obtained during screening. Patients receiving a diagnosis of indeterminate colitis, CD, or clinical findings suggestive of CD (such as a fistula or granuloma on biopsy) were excluded from the study.

Concurrent therapy was not required at enrollment for (1) patients in ACT 1 and ACT 2 who had had no response to corticosteroids within the preceding 18 months or who could not tolerate corticosteroids, (2) patients in either study who had had no response to azathioprine or mercaptopurine within the preceding five years or who could not tolerate these drugs, and (3) patients in ACT 2 who had had no response to medications containing 5-aminosalicylates within the preceding 18 months or who could not tolerate such drugs.

Rectally administered corticosteroids or medications containing 5-aminosalicylates were not permitted

within two weeks before screening. Patients who had been previously exposed to IFB or to any other anti-TNF agent were excluded.

Eligible patients were randomly assigned, in a 1:1:1 ratio, to receive intravenous (IV) infusions of IFB at a dose of 5 mg/kg or 10 mg/kg or placebo at Weeks 0, 2, and 6 and then every eight weeks through Week 22 in ACT 2 or through Week 46 in ACT 1. Patients were followed through Week 30 in ACT 2 and through Week 54 in ACT 1.

Each study used central randomization with a dynamic treatment allocation stratified according to the investigational site and according to whether patients had UC that was refractory to corticosteroid therapy. Patients were considered to have UC that was refractory to corticosteroids if their symptoms of UC had not improved after they received the equivalent of at least 40 mg of prednisone daily, administered orally for at least two weeks or intravenously for at least one week.

Doses of concomitant medications remained constant except for corticosteroids, which were tapered by 5 mg weekly after Week 8 until a dose of 20 mg/day was reached. Thereafter, the dose was reduced by 2.5 mg weekly until discontinuation of therapy.

Results¹³

ACT 1

In ACT 1, significantly higher proportions of patients receiving IFB 5 mg/kg (69.4%) and 10 mg/kg (61.5%) achieved clinical response at Week 8, compared with placebo-treated patients (37.2%; $P < .001$ for both). In addition, at Week 30, 52.1% of patients in the 5-mg/kg and 50.8% of patients in the 10-mg/kg IFB treatment group were in clinical response versus 29.8% of placebo-treated patients ($P < .001$ and $P = .002$, respectively).

By Week 54, 45.5% of patients in the IFB 5-mg/kg group and 44.3% of patients in the IFB 10-mg/kg group achieved clinical remission, compared with 19.8% of patients in the placebo group ($P < .001$ for both).

At Week 8, 38.8% and 32.0% of patients treated with IFB 5 mg/kg and 10 mg/kg, respectively, were in clinical remission, compared with 14.9% of placebo-treated patients ($P < .001$ and $P = .002$, respectively). These differences in remission rates at Week 30 were statistically significant (33.9%, 5 mg/kg; 36.9%, 10 mg/kg vs. 15.7%, placebo; $P < .001$ for both).

By Week 54, 34.7% of patients receiving IFB 5 mg/kg and 34.4% of patients in the IFB 10-mg/kg group were in clinical remission, compared with 16.5% of placebo patients ($P = .001$).

Remission was defined as a Mayo score of 2 points or less with no individual subscore above 1.

Mucosal healing was achieved at Week 8 in 62% and

59% of patients receiving IFB 5 mg/kg and 10 mg/kg, respectively, compared with 33.9% of placebo-treated patients ($P < .001$). This difference in mucosal healing at Week 30 was also statistically significant (50.4%, 5 mg/kg; 49.2%, 10 mg/kg vs. 24.8%, placebo; $P < .001$ for both).

By Week 54, 45.5% of patients in the 5-mg/kg group and 46.7% of patients in the 10-mg/kg group had maintained mucosal healing, compared with 18.2% of placebo patients ($P < .001$ for both).

Mucosal healing was defined as an endoscopy subscore of 0 or 1.

ACT 2

In ACT 2, significantly higher proportions of patients receiving IFB 5 mg/kg (64.5%) and 10 mg/kg (69.2%) were in clinical response at Week 8, compared with 29.3% who received placebo ($P < .001$ for both).

At Week 30, 47.1% of patients receiving IFB 5 mg/kg and 60.0% of those receiving 10 mg/kg were had clinical responses, compared with 26.0% of patients receiving placebo ($P < .001$ for both). Clinical remission was achieved at Week 8 in 33.9% and 27.5% of patients receiving IFB 5 mg/kg and 10 mg/kg, respectively, compared with 5.7% of placebo-treated patients ($P < .001$ for both). Remission was defined as a Mayo score of 2 points or less with no individual subscore below 1. Differences in remission rates at Week 30 were statistically significant (25.6%, 5 mg/kg; 35.8%, 10 mg/kg; 11%, placebo; $P = .003$ and $P < .001$).

Mucosal healing was achieved at Week 8 in 60.3% and 61.7% of patients receiving IFB 5 mg/kg and 10 mg/kg, respectively, compared with 30.9% of placebo-treated patients ($P < .001$ for both). Mucosal healing was defined as an endoscopy subscore of 0 or 1.

Mucosal healing at Week 30 was achieved in 46.3% and 56.7% of patients receiving IFB 5 and 10 mg/kg, respectively, compared with 30% of placebo-treated patients ($P = .009$ and $P < .001$).

Discontinuation of Steroids in ACT 1 and ACT 2

The proportion of patients who were in clinical remission and who had discontinued corticosteroids at Week 30 in both studies and at Week 54 in ACT 1 was higher in the IFB groups than in the placebo groups. Similarly, the decreases in the median daily corticosteroid doses were greater among patients in the IFB groups than among those in the placebo groups.

Safety Considerations¹³

In both ACT 1 and ACT 2, the proportion of patients with ADEs was similar in the placebo group and in the two IFB groups. In ACT 1, serious ADEs occurred in 25.6% of patients receiving placebo, in 21.5% of patients receiving IFB 5 mg, and in 23.8% of patients receiving IFB 10 mg. In ACT 2, the rates of serious ADEs were

19.5% with placebo, 10.7% with IFB 5 mg/kg, and 9.2% with IFB 10 mg/kg. In both studies, serious ADEs were most commonly related to the GI system.

In ACT 1, similar numbers of patients in each group discontinued treatment because of an ADE; in ACT 2, more patients in the placebo group than in the two IFB groups discontinued treatment because of an ADE.

Among ADEs in ACT 1, prostatic adenocarcinoma developed in one patient with a two-year history of elevated prostate-specific antigen (PSA) levels, and colonic dysplasia developed in one patient; both patients had received IFB 5 mg. Basal cell carcinoma developed in one patient who was treated with IFB 10 mg. In ACT 2, basal cell carcinoma developed in one patient who received placebo, and rectal adenocarcinoma developed in one patient who received IFB 5 mg.

Only three neurological events occurred, all of them in patients who received IFB. In ACT 1, optic neuritis developed in one patient who received IFB 5 mg. After ACT 2 was completed, a multifocal motor neuropathy with conduction block syndrome developed in one patient who received IFB 10 mg, and optic neuritis developed in one patient who received IFB 5 mg.

In both studies, the development of antinuclear antibodies and anti-double-stranded DNA antibodies was more common among the IFB patients than among the placebo patients. Only one patient had a lupus-like reaction; this patient was enrolled in ACT 2 and received IFB 5 mg.

The incidence of infections was similar among the groups in both studies. In ACT 1, serious infections occurred in five patients (4.1%) in the placebo group, three patients (2.5%) in the IFB 5-mg group, and eight patients (6.6%) in the group receiving IFB 10 mg. In ACT 2, serious infections occurred in one patient (0.8%) in the placebo group, two patients (1.7%) in the group receiving IFB 5 mg, and three patients (2.5%) in the group receiving IFB 10 mg.

In ACT 1, tuberculosis (TB) occurred in one patient who had been treated with IFB 10 mg. *Histoplasma* pneumonia developed in one patient in the group receiving IFB 5 mg during the ACT 2 extension. The extension was a study phase in which patients who completed the 30-week, double-blind phase—and whom the investigators thought would benefit from continued treatment—were enrolled and who continued to receive the study agent to which they had been randomly assigned. The disease progressed to acute respiratory distress syndrome, and the patient died.

In ACT 1, infusion reactions occurred in 13 patients (10.7%) in the placebo group, 12 patients (9.9%) in the IFB 5-mg group, and 15 patients (12.3%) in the IFB 10-mg group. A possible delayed hypersensitivity reaction occurred in two patients (1.7%) in the placebo group and in two patients (1.7%) in the IFB 5-mg group.

In ACT 2, infusion reactions occurred in 10 patients (8.1%) in the placebo group, 14 patients (11.6%) in the IFB 5-mg group, and 14 patients (11.7%) in the IFB 10-mg group. A possible delayed hypersensitivity reaction occurred in one patient (0.8%) in the IFB 10-mg group.

At Week 54 in ACT 1, 35.7% of patients with positive test results for IFB antibodies (5 of 14) experienced infusion reactions, compared with 9.8% of patients with negative or inconclusive findings (21 of 215). In ACT 2, at Week 30, 50.0% of patients with positive test results for antibodies against IFB (6 of 12) had infusion reactions, compared with 9.7% of patients with negative or inconclusive findings (17 of 176).

No patient in either study who had a positive test for antibodies had a serious infusion reaction or an anaphylactic reaction. Only one patient in the IFB 5-mg group in ACT 1 who tested positive for antibodies had a serious delayed hypersensitivity reaction.

PLAQUE PSORIASIS

European Infliximab for Psoriasis (Remicade) Efficacy and Safety Study: EXPRESS²³

EXPRESS was a phase 3 multicenter, double-blind placebo-controlled trial with the primary objective of evaluating the safety and efficacy of IFB induction and maintenance therapy in patients with plaque-type psoriasis.

Patients had a diagnosis of plaque-type psoriasis for at least six months, were candidates for phototherapy or systemic therapy, had a Psoriasis Area Severity Index (PASI) score of at least 12, and had at least 10% of their total body surface area (BSA) affected by psoriasis. Those with a history or risk of serious infection, lymphoproliferative disease, or active tuberculosis were ineligible, and previous treatment with IFB or any other TNF- α antagonists was not allowed.

Patients with guttate, pustular, or erythrodermic psoriasis were excluded from the study.

Concomitant topical treatment, phototherapy, or any systemic treatment that could affect psoriasis was not allowed up to Week 50, with the exception of 2.5% hydrocortisone, or equivalent, applied topically to the face or groin, or both, after Week 10.

Trial Endpoints

The primary endpoint for this trial was the proportion of patients achieving a PASI 75 response at Week 10. Major secondary endpoints included PASI 75 responses at Week 24 and a Physician's Global Assessment (PGA) score of "Minimal" or "Cleared" at Week 10.

Efficacy data from all patients were analyzed according to assigned treatment groups. For patients in the placebo group, only patients who crossed over to receive IFB were included in efficacy summaries for visits after Week 24.

Safety data were summarized by the actual treatment received in patients who had had at least one dose of study agent. PASI 75 responses, as well as PASI 50 (50% improvement) and PASI 90 (90% improvement) responses, were analyzed at Week 10, on an intention-to-treat basis.

Patients were regarded as not achieving the endpoints if they discontinued study treatment because of lack of efficacy or loss of response or were treated with prohibited treatments before Week 10. In addition, patients who did not return for assessment or had insufficient data to calculate the PASI at Week 10 were regarded as not achieving PASI 50, PASI 75, or PASI 90.

An intention-to-treat analysis was not done for other efficacy analyses. Instead, the following data handling rules were applied (prespecified analysis): in patients who discontinued the study agent because of lack of efficacy or loss of response or who started disallowed medication, baseline values were used for continuous

variables, or the patients were regarded as not achieving the endpoints for binary responses, irrespective of the observed data. For other patients, observed data were used.

In the prespecified analysis of PASI response over time, all observed data were used irrespective of whether the drug was given. In the per-protocol analysis, which was done *post hoc*, patients must have completed the induction phase to be included in the analysis. Additionally, data after two missed infusions or after study infusion discontinuation were excluded. In the per-protocol analysis, patients who discontinued because of lack of efficacy or loss of response, or who started disallowed nontopical medication were deemed non-responders.

Methods

Three hundred one patients were randomized to receive 5-mg/kg IFB infusions at Weeks 0, 2, and 6, followed by a maintenance regimen of 5 mg/kg of IFB every eight weeks through Week 46 and placebo infusions at Weeks 24 and 26 to maintain the blinding. Seventy-seven patients were randomly assigned to the placebo group and received placebo infusions at Weeks 0, 2, 6 and every eight weeks thereafter, followed by a placebo maintenance regimen every eight weeks through Week 22.

At Week 24, patients in the placebo group were crossed over to IFB therapy and received induction therapy with IFB 5 mg/kg in a double-blind fashion at Weeks 24, 26, and 30, followed by a maintenance regimen of IFB 5 mg/kg every eight weeks through Week 46. Patients were evaluated for safety, efficacy at Weeks 0, 2, 6, 10, 14, 22, 24, 26, 30, 38, 46, and 50. The final blood draw was taken at Week 66.

Results

The proportion of patients who achieved the primary endpoint of a PASI 75 response at Week 10 was significantly greater in the IFB group than in the placebo group (80% vs. 3%, $P < .0001$).

At six months, based on the prespecified analysis, the proportion of patients achieving PASI 50, 75, and 90 responses was consistent with the responses seen at Week 10.

Based on the prespecified analysis, six out of 10 patients achieved a PASI 75 response at Week 50. In the per-protocol analysis, seven out of 10 IFB-treated patients achieved a PASI 75 response at Week 50.

The therapeutic response in IFB-treated patients was rapid, with significant differences ($P < .0001$) recorded between the treatment groups as early as Week 2 for the proportion of patients achieving PASI 50. By Week 6, significantly more IFB-treated patients than placebo-treated patients achieved PASI 75 and PASI 90 ($P < .0001$). The PASI 75 and PASI 90 responses

were sustained through Week 24.

Of those patients receiving IFB 5 mg/kg, 83% had a PGA score of "Minimal" or "Cleared" at Week 10 versus 4% for placebo ($P < .0001$).

Safety

Through Week 24, the proportion of patients who experienced at least one adverse event was slightly higher in the IFB group (82%) than in the placebo group (71%). Similar proportions of patients in each treatment group reported infections and infusion reactions.

Three serious infections (i.e., defined as any infection meeting the regulatory definition for a serious adverse event) were reported in IFB-treated patients. In addition, three patients in the IFB group had delayed hypersensitivity reactions, generally characterized by myalgia, arthralgia, fever, or rash, which improved within two weeks in all but one patient for whom follow-up information was not available.

There were no demyelinating events, tuberculosis, or serious opportunistic infections and no new-onset congestive heart failure or hematological events of interest (pancytopenia, aplastic anemia, agranulocytosis).

Through Week 24, two patients in the IFB group were reported to have a lupus-like syndrome with arthralgias and anti-double-stranded DNA antibodies. Through Week 50, four serious infusion reactions were reported in the IFB-treated patients.

No clinically significant changes were noted in hematological or chemical values, with the exception of aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Through Week 24, 6% and 2% of patients in the IFB group had generally asymptomatic, markedly abnormal increases in ALT and AST levels, respectively (i.e., defined as more than 150 units/liter and an increase of 100% or more from baseline), compared with none in the placebo group. No patients had a markedly abnormal bilirubin (>3.0 mg/dl and $\geq 100\%$ increase) or alkaline phosphatase (>250 IU/liter and $\geq 100\%$ increase) value, and no adverse events of jaundice or hyperbilirubinemia were reported. These increases resolved with continuation or interruption of treatment and, in certain cases, discontinuation of treatment; however, most patients were able to complete the infusions.

One patient in the IFB treatment group died 25 days after the Week 2 infusion as a result of sepsis secondary to necrotizing fasciitis. This patient experienced a severe burn on his hand about one week before hospital admission, but he did not seek medical attention. On admission, this patient was given a diagnosis of cellulitis and was treated with an IV cephalosporin, but he died 12 hours later.

Evaluation of Infliximab for Psoriasis in a Remicade Efficacy and Safety Study: EXPRESS II²⁴

EXPRESS II was a multicenter, randomized, double-blind, placebo-controlled trial with the primary objective of comparing the efficacy and safety of continuous (every-eight-week) and intermittent (as-needed) maintenance regimens of IFB.

Trial Endpoints

The primary efficacy endpoint was the proportion of patients achieving PASI 75 at Week 10. Other endpoints included the proportion of patients with a PGA score of 1 (“Clear”) or “2 (Excellent)” at Week 10 and the average percent improvement from baseline in PASI between Weeks 16 and 30 and between Weeks 16 and 50. Key efficacy parameters evaluated through Week 50 included PASI 75, at least a 90% improvement in PASI (PASI 90) and PGA scores.

An *ad hoc* analysis was also performed to compare the average percent improvement in PASI from baseline between Week 2 and Week 50, and between 3 mg/kg every eight weeks and 5 mg/kg every eight weeks.

IFB safety and tolerability were assessed by monitoring adverse events, vital signs, and laboratory parameters through Week 50. An infusion reaction was defined in the study protocol as any adverse event occurring during or within one hour after the administration of the study agent.

Methods

Investigators enrolled 835 adult patients with plaque psoriasis at 63 sites in the U.S., Canada, and Europe. All patients provided written informed consent, and institutional review boards or ethics committees at all sites approved the study.

Eligible patients were candidates for phototherapy or systemic therapy; had a PASI score of 12 or more with at least 10% BSA involvement; and had no history of serious infection, lymphoproliferative disease, or active tuberculosis (TB). Previous treatment with IFB was not allowed.

Concomitant topical therapy, phototherapy, or systemic therapy for psoriasis was prohibited throughout the study, with the exception of low-potency topical corticosteroids for the face and groin after Week 10. The use of disease-modifying antirheumatic drugs was not permitted during the study, but stable doses of non-steroidal anti-inflammatory drugs (NSAIDs) were allowed.

The induction phase of the trial was placebo-controlled. Eligible patients were randomly selected to receive induction infusions of IFB 3 mg/kg or 5 mg/kg or placebo at Weeks 0, 2, and 6, with the investigational site as a stratum. At Week 14, patients in the IFB induction groups were randomly assigned again to

either every-eight-week continuous maintenance therapy or intermittent as-needed maintenance therapy, with the investigational site and Week 10 PASI responder status (i.e., whether or not PASI 75 was achieved) as strata.

Patients assigned to the every-eight-week maintenance continued to receive the original IFB dose, with infusions administered at eight-week intervals (Weeks 14, 22, 30, 38, and 46).

Patients assigned to as-needed maintenance received the original IFB dose at visits during which observed improvement in PASI from baseline was less than 75%, and they received placebo if PASI improvement was at least 75%.

Maintenance visits occurred monthly, permitting infusions as frequently as every four weeks for patients in the as-needed groups. Patients in the placebo-induction group crossed over to receive IFB 5 mg/kg at Weeks 16, 18, and 22, and every eight weeks thereafter.

Placebo infusions were administered to all groups as needed to preserve the blind.

Results

Of 835 enrolled patients, 313 were randomly selected to receive induction therapy with IFB 3 mg/kg, 314 to IFB 5 mg/kg, and 208 to placebo. Through Week 50, 252 patients (30.2%) permanently discontinued the study agent. Of the 595 patients overall who underwent a second randomization at Week 14, 162 (27.2%) discontinued the study treatment before Week 50. Fewer patients in the 3-mg/kg as-needed treatment group completed the study treatment when compared with the other treatment groups.

The demographic characteristics of the induction treatment groups were similar, and the mean percentage of involved BSA, types of prior therapy used, and mean baseline PASI scores were comparable.

The clinical effect of IFB was rapid in onset, with statistically significant proportions of IFB-treated patients in both dose groups, compared with placebo, achieving PASI 75 status as early as Week 2 ($P \leq .001$ for both comparisons).

At Week 10, PASI 75 status was achieved by 70.3% and 75.5% of patients in the IFB 3-mg/kg and 5-mg/kg induction groups, respectively, compared with 1.9% of patients in the placebo group ($P < .001$).

Similarly, 69.8% and 76% of patients in the IFB 3-mg/kg and 5-mg/kg induction groups, respectively, achieved a PGA score of “Clear” or “Excellent” at Week 10, compared with 1% of the placebo group ($P < .001$).

Through Week 50, mean total daily doses of IFB received did not vary substantially between the every-eight-week groups and the corresponding as-needed regimen within each dose (i.e., 22.1 mg/kg for the 3-mg/kg every-eight-week group, compared with 20.1 mg/kg for the 3-mg/kg as-needed group. The corre-

sponding mean total doses for the 5-mg/kg groups were 37.1 mg/kg and 30.2 mg/kg).

Through Week 50, PASI 75 response was better achieved with every-eight-week than with as-needed maintenance therapy, and it was again best achieved by patients in the IFB 5-mg/kg every-eight-week group.

At Week 50, for all patients randomly selected at Week 14, PASI 75 was achieved by 54.4% and by 43.8%, respectively, of patients receiving 5 mg/kg and 3 mg/kg on an every-eight-week basis, compared with 38.1% and 25.4% of patients receiving 5mg/kg and 3 mg/kg, respectively, on an as-needed basis.

The highest proportions of patients who achieved a PASI 90 response at Week 50 were again seen in the IFB 5-mg/kg and 3-mg/kg every-eight-week maintenance groups (34.3% and 25%, respectively, compared with 10.4% and 9.5% for the 5-mg/kg and 3-mg/kg as-needed maintenance groups.)

Average percent improvement in PASI from baseline between Week 2 and Week 50 was also compared between patients receiving IFB 3 mg/kg every eight weeks and those receiving 5 mg/kg every eight weeks. The median (mean; IQ range) of the average percent improvement in PASI between Week 2 and Week 50 was 69.1% (65.5%; 51%–84.7%) for patients who received 3 mg/kg every eight weeks, compared with 81.3% (73.5%; 63.4–89.4%) for those who received 5 mg/kg every eight weeks ($P = .003$).

PASI response in the 183 placebo patients who crossed over to receive IFB 5 mg/kg at Week 16 paralleled results in the patients who were randomly selected to receive IFB 5 mg/kg at baseline.

The proportion of patients achieving PASI 75 at Week 26, 10 weeks after crossing over to IFB 5 mg/kg, was 76.2%.

Safety

Week 0 to Week 14

Through Week 14, adverse events were more frequent in both IFB induction groups than in the placebo group; however, the types of adverse events were similar.

The proportion of patients in the 5-mg/kg group who experienced at least one serious adverse event (ADE) was comparable to that in the placebo group, whereas the proportion in the 3-mg/kg group was slightly lower.

The incidence of rhinitis was slightly higher with active treatment (placebo, 0.5%; 3 mg/kg, 3.2%; 5 mg/kg, 2.9%), and there was a trend toward higher incidences of sinusitis with IFB, compared with placebo, especially with the higher IFB dose (placebo, 1.4%; 3 mg/kg, 2.9%; 5 mg/kg, 6.4%). The incidence of cough in the IFB 3-mg/kg group was higher than that in both the placebo and IFB 5-mg/kg groups.

Treatment was discontinued because of ADEs (most commonly psoriasis, nausea, or dyspnea) by 4.5%, 5.1%,

and 2.4% of patients in the 3-mg/kg, 5-mg/kg, and placebo groups, respectively.

The proportion of patients reporting infections was similar for the IFB induction and placebo groups, with upper respiratory tract infection the most commonly reported event for all groups.

Infusion reactions, defined as any ADEs occurring during or within one hour of study drug infusion, occurred more often in the 3-mg/kg group (11.5%) than in the 5-mg/kg group (9.6%). Most infusion reactions were of mild or moderate severity.

Week 14 to Week 50

Through Week 50, the incidence of ADEs, serious ADEs, and infections was comparable among the four IFB maintenance treatment groups. Maintenance-phase infusion reactions occurred more often with as-needed than with every-eight-week infusions for a given dose and occurred most often within the 3-mg/kg as-needed dose group. Most infusion reactions were classified as mild or moderate.

Through Week 50

Two cases of TB were reported in the combined IFB group (one patient who received 3 mg/kg during the induction phase only and one randomly selected to receive 5 mg/kg as needed). Both cases occurred in patients who had negative baseline purified protein derivative (PPD) tuberculin skin tests. Both patients also had chest radiographs interpreted as normal at baseline. No other serious opportunistic infections were reported.

Twelve malignancies were reported in 12 patients in the IFB groups. These included a breast carcinoma, a salpingeal adenocarcinoma in a postmenopausal patient, a squamous cell skin carcinoma, and nine basal cell skin carcinomas.

All of the 10 patients with skin carcinoma had antecedent exposure to narrow-band ultraviolet B (eight patients), psoralen plus ultraviolet A (two patients), or both (two patients). No malignancies were reported in the placebo-treated patients during the placebo-controlled induction phase.

Increases in ALT and AST considered “markedly abnormal” (predefined for this study as elevations above 150 IU/liter and an increase of 100% or more from baseline) occurred in 4.9% and in 3.1% of patients, respectively, in the combined IFB treatment groups.

Lupus-like syndrome was reported in two IFB-treated patients, one of whom presented with arthralgia, joint stiffness, and pulmonary symptoms, and the other with central nervous system vasculitis. Hydralazine exposure, considered possibly contributory, was also reported for the latter patient.

Improvement was seen in both patients after discontinuation of hydralazine and/or IFB and appropri-

ate treatment. Lupus-like syndrome also occurred in one patient who received only placebo therapy and who tested positive for antinuclear antibodies at baseline.

There were no central demyelinating events; however, one patient developed prolonged extremity muscle weakness with a diagnosis of peripheral neuropathy considered possibly related to the study agent. The patient subsequently recovered.

There were no patient deaths during the study. One patient, a 41-year-old man with no known predisposition for cardiac disease, suffered a fatal myocardial infarction nine months after discontinuing IFB.

Serious infusion reactions were rare events, occurring in five patients in the combined IFB treatment groups (including placebo crossover patients). There were nine reports of possible delayed hypersensitivity reaction, defined as any adverse event involving myalgia and/or arthralgia, with fever and/or rash, occurring one to 14 days after an infusion of study drug; four of these reactions were considered serious.

Study of Psoriasis with Infliximab (Remicade) Induction Therapy (SPIRIT)²⁵

SPIRIT was a multicenter, randomized, double-blind, placebo-controlled trial with the objectives of evaluating the efficacy and safety of IFB induction therapy for patients with severe plaque psoriasis.

Trial Endpoints

The primary endpoint of the double-blind study was to assess the safety and efficacy of a three-dose induction regimen of IFB for the treatment of severe psoriasis. The trial was also designed to test whether IFB could safely be re-administered to patients 20 weeks after completion of the induction regimen.

Methods

A total of 249 patients were randomly assigned to treatment with placebo (51 patients), IFB 3 mg/kg (99 patients), or IFB 5 mg/kg (99 patients). One patient was randomly assigned to receive IFB 3 mg/kg but was not treated. The treatment groups were well balanced with respect to demographics and baseline characteristics.

Trial Design

This randomized, double-blind, placebo-controlled trial was conducted from 2001 to 2003 in 24 centers in the U.S. Eligible patients were randomly assigned, in a 1:2:2 ratio, to IV infusions of placebo, IFB (3 mg/kg) or IFB 5 mg/kg and were treated at Weeks 0, 2, and 6.

At Week 26, patients with a static PGA of moderate to severe disease activity ($PGA \geq 3$) were eligible for a single additional IV infusion of their assigned study treatment. All systemic or light therapies for psoriasis were stopped one month before and during the trial. No topical therapies for psoriasis were allowed two weeks before and during the trial except emollients and shampoos containing tar or acid.

Results

At Week 10, 71.7% of patients ($n = 71$) receiving IFB 3 mg/kg and 87.9% of patients ($n = 87$) receiving IFB 5 mg/kg achieved PASI 75 scores, compared with 5.9% ($n = 3$) of placebo-treated patients. At the same point in time, 87.9% ($n = 89$) of patients receiving IFB 3 mg/kg and 98% ($n = 97$) of patients receiving IFB 5 mg/kg achieved PGA scores of "Mild," "Minimal," or "Cleared," compared with 45.1% ($n = 23$) of placebo patients.

To assess the duration of response, the study authors monitored patients for 20 weeks after the last infusion in the induction period. The maximum response was observed at Week 10 for both IFB treatment groups.

This high level of response was maintained until Week 14 in the IFB 5-mg/kg group but started to decline in the 3-mg/kg group after Week 10. A decline in response was observed in the 5-mg/kg group after Week 14.

TABLE 8 Incidence of Adverse Events Through Week 30 in the SPIRIT Study

Category	Infliximab			
	Placebo	3 mg/kg	5 mg/kg	Combined
No. of patients treated	51	98	99	197
Average follow-up (weeks)	20.0	29.6	30.7	30.2
No. of patients with ≥ 1 adverse event (%)	32 (62.7%)	76 (77.6%)	78 (78.8%)	154 (78.2%)
No. of patients with serious adverse events (%)	0 (0.0%)	4 (4.1%)	8 (8.1%)	12 (6.1%)
No. of patients with reasonably related serious adverse events	0 (0.0%)	2 (2.0%)	2 (2.0%)	4 (2.0%)
No. patients with serious infections (%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.5%)
No. of patients with serious infusion reactions (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No. of patients with infusion reactions (%)	1 (2.0%)	18 (18.4%)	22 (22.2%)	40 (20.3%)
Total No. of infusions	147	341	343	684
No. of infusions with infusion reactions (%)	1 (0.7%)	19 (5.6%)	26 (7.6%)	45 (6.6%)
Mild	1 (0.7%)	11 (3.2%)	18 (5.2%)	29 (4.2%)
Moderate	0 (0.0%)	8 (2.3%)	6 (1.7%)	14 (2.0%)
Severe	0 (0.0%)	0 (0.0%)	2 (0.6%)	2 (0.3%)
Patients newly positive for antinuclear antibodies: No./total No. (%)	1/44 (2.3%)	19/83 (22.9%)	20/80 (25.0%)	39/163 (23.9%)
Patients newly positive for antibodies against dsDNA: No./total No. (%)	1/48 (2.1%)	3/91 (3.3%)	4/94 (4.3%)	7/185 (3.8%)
Patients with antibodies to infliximab: No./total No. (%)	NA	21/76 (27.6%)	17/87 (19.5%)	38/163 (23.3%)

dsDNA = double-stranded DNA; NA = not applicable.
 From Gottlieb AB, Evans R, Li S, et al. *J Am Acad Dermatol* 2004;51:534–542.²⁵

Safety

The incidence of adverse events through Week 30 is illustrated in Table 8.

The incidence of antibodies to IFB through Week 26 was higher for patients receiving 3 mg/kg of IFB (27%) compared with those receiving 5 mg/kg (20%). Overall, nine of 38 (24%) patients with antibodies to IFB experienced infusion reactions through Week 26 compared

with 25 of 116 (22%) patients evaluated as antibody-negative. Of the patients with appropriate samples who were retreated at Week 26 after the 20-week interval without treatment, five of 22 patients (23%) who were positive for antibodies to IFB experienced an infusion reaction on re-treatment compared with 6 of 73 patients (8%) evaluated as negative for antibodies to IFB.

P&T Committee Considerations

Generally speaking, there are a number of valid considerations that P&T committees must contemplate before making a final decision to include or remove a drug from the formulary. Criteria may include drug safety, efficacy, the need for the agent, potential misuse, side effects, the availability of other agents with similar therapeutic effects, and cost.¹⁶ This section evaluates P&T committee considerations that may apply to IFB. Included are important measures for drug assessment.

EFFICACY^{6,14-21}

Rheumatoid Arthritis

The ATTRACT findings indicated that IFB could produce a rapid reduction in disease activity in patients whose RA was inadequately controlled with therapeutic doses of MTX. Participants achieved a significant improvement in more than 50% of cases observed. Maintenance therapy with IFB at its lowest dose (3 mg/kg every eight weeks), when combined with MTX, resulted in sustained responses for up to 30 weeks, and no increase in serious ADEs was observed. The number of IFB reactions was low and did not increase with repeated infusions.

IFB/MTX not only resulted in improvements in the signs and symptoms of RA effectively but also improved patients' quality of life and brought about significant improvements in biochemical measurement of inflammation (CRP and ESR). Furthermore, combination therapy prevented the progression of joint-damage characteristics and resulted in improved radiographic scores. The inhibited progression of joint damage and improvement in patient function, as measured by the HAQ or by the SF-36, were also noted.¹⁴

The degree of improvement observed translates into an increase in functional activities that have the potential to reduce rates of disability and health care costs. Therapy was generally well tolerated; the frequency of serious infection was statistically no greater with combination therapy than with monotherapy.

Although the administration of IFB is associated with the development of autoantibodies, which may alter the overall pharmacokinetics or cause a lupus-like syndrome (e.g., with discoid), this effect rarely occurred in the aforementioned trials. Despite the

potential for autoantibody formation, the pharmacokinetic profile remained stable.

Crohn's Disease

In patients with Crohn's disease (CD), IFB as maintenance therapy sustained clinical remission and reduced patients' exposure to corticosteroids. More than twice as many patients who received maintenance therapy with IFB continued in clinical remission from Week 14 to Week 54, compared with those who received placebo. IFB also produced a rapid response that had not been seen with MTX and azathioprine.

IFB has also been effective for patients with draining fistulas; therapeutic responses were rapid in controlling disease activity. Closure of fistulas was also sustained in patients who had not responded previously to treatment with other agents.

Active Crohn's Disease in Pediatric Patients

The proportion of pediatric patients achieving a clinical response at Week 10 compared favorably with the proportion of adults achieving a clinical response in ACCENT I. At both Week 30 and Week 54, the proportion of patients achieving a clinical response was greater in the every-8-week treatment group than in the every-12-week treatment group. At both Week 30 and Week 54, the proportion of patients in clinical remission was also greater in the every-8-week treatment group than in the every-12-week treatment group (Table 9).

At Week 54, the proportion of patients able to discontinue corticosteroids while in remission was 46% for the every-8-week maintenance group and 17% for the every-12-week maintenance group.

Ankylosing Spondylitis

IFB demonstrated substantial improvement in several measures of disease activity, physical function, and quality of life. In general, the IFB patients experienced a shorter duration of disease and decreased disease progression. They showed significant improvement in range of motion and in BASMI and ASAS responses.

IFB was generally well tolerated. The overall ADE profile was comparable with that reported previously for patients with RA. This therapy provides an effective treatment option that has a significant impact on early disease processes.

Psoriatic Arthritis

In IMPACT 2, IFB 5 mg/kg significantly improved active psoriatic arthritis, including dactylitis and enthesopathy, and associated psoriasis through 24 weeks.

The ACR response was evident as early as the second week, and responses were maintained throughout the trial. Patients who received IFB experienced rapid, substantial, and sustained improvement in psoriasis, as measured by PASI improvement and by target lesion scores in those with less significant, as well as with more significant disease. The IMPACT 2 results confirm that treatment with IFB is effective in patients with psoriatic arthritis.

Ulcerative Colitis

The approval of IFB is based on positive results seen in two randomized, placebo-controlled pivotal phase 3 clinical trials, ACT 1 and ACT 2, which were conducted to evaluate the safety and efficacy of IFB in people with active, moderate-to-severe UC.

In both trials, greater percentages of patients in both IFB groups achieved a clinical response, a sustained clinical response (a response at both Weeks 8 and 30), clinical remission, and other assessed clinical outcomes compared with the placebo group.

Of patients taking corticosteroids at baseline, greater proportions of patients in the IFB treatment

groups were in clinical remission and able to discontinue corticosteroids at Week 30, compared with the patients in the placebo treatment groups (22% in IFB treatment groups vs. 10% in placebo group in ACT 1; 23% in IFB treatment groups vs. 3% in placebo group in ACT 2).

The IFB-associated response was generally similar in the 5-mg/kg and 10-mg/kg dose groups.

Plaque Psoriasis

The safety and efficacy of IFB were assessed in three randomized, double-blind, placebo-controlled studies in patients who were 18 years of age and older with chronic, stable plaque psoriasis involving a body surface area (BSA) of 10% or greater and a minimum PASI score of 12 and who were candidates for systemic therapy or phototherapy.

In all three studies, the primary endpoint was the proportion of patients who achieved a reduction in scores of at least 75% from baseline at Week 10 by the PASI (PASI 75). In EXPRESS and SPIRIT, another evaluated outcome included the proportion of patients who achieved a score of “Cleared” or “Minimal” by the static PGA (sPGA).

EXPRESS II also evaluated the proportion of patients who achieved a score of “Clear” or “Excellent” by the relative PGA (rPGA). Overall lesions were

TABLE 9 Response and Remission in Study Peds Crohn's

	5 mg/kg IFB	
	Every-8-Week Treatment Group	Every-12-Week Treatment Group
Patients randomized	52	51
Clinical response ¹		
Week 30	73%*	47%
Week 54	64%*	33%
Clinical remission ²		
Week 30	60%†	35%
Week 54	56%*	24%

¹ Defined as a decrease from baseline in the Pediatric Crohn's Disease Activity Index (PCDAI) score of ≥15 points and total score of ≤30 points.

² Defined as a PCDAI score of ≤ 10 points.

* P value < .01

† P value < .05

graded with consideration to the percentage of body involvement as well as overall induration, scaling, and erythema.

Treatment success, defined as “Clear” or “Excellent,” consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present).

In EXPRESS, in the subgroups of patients with more extensive psoriasis who had previously received phototherapy, 85% of patients receiving IFB 5 mg/kg achieved a PASI 75 at Week 10, compared with 4% of patients receiving placebo.

In EXPRESS II, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 72% and 77% of patients receiving IFB 3 mg/kg and 5 mg/kg achieved a PASI 75 at Week 10, respectively, compared with 1% of patients receiving placebo.

In EXPRESS II, among patients with more extensive psoriasis who had not responded to or who were intolerant of phototherapy, 70% and 78% of patients receiving IFB 3 mg/kg and IFB 5 mg/kg, respectively, achieved a PASI 75 at Week 10, compared with 2% of patients receiving placebo.

In EXPRESS II, maintenance of response was studied in a subset of 292 and 297 patients treated with IFB in the 3-mg/kg and 5-mg/kg groups, respectively. Stratified by PASI response at Week 10 and by investigational site, patients in the active treatment groups were again randomly assigned to either scheduled or as-needed maintenance therapy, beginning at Week 14. The groups who received a maintenance dose every eight weeks appeared to have a greater percentage of patients maintaining a PASI 75 through Week 50, compared with patients who received the as-needed doses. The best response was maintained with the 5-mg/kg every-eight-week dose.

The results of EXPRESS through Week 50 in the 5-mg/kg every-eight-week maintenance dose group were similar to the results from EXPRESS II.

INDICATIONS AND USAGE¹⁴

Rheumatoid Arthritis

IFB, in combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.

Crohn's Disease

IFB is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active CD who have had an inadequate response to conventional therapy.

IFB is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD.

Ankylosing Spondylitis

IFB is indicated for reducing signs and symptoms in patients with active AS.

Psoriatic Arthritis

IFB is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

Ulcerative Colitis

IFB is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active UC who have had an inadequate response to conventional therapy.

Plaque Psoriasis

IFB is indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. IFB should be administered only to patients who will be closely monitored and who will have regular follow-up visits with a physician.

SAFETY¹⁴

P&T committee members should be aware of the following contraindications, warnings, precautions, drug interactions, and other considerations associated with IFB.

Boxed Warnings

Risk of Infections

Patients treated with IFB are at increased risk for infections, including progression to serious infections leading to hospitalization or death. These infections have included bacterial sepsis, TB, and invasive fungal and other opportunistic infections. Patients should be educated about the symptoms of infection, should be closely monitored for signs and symptoms of infection during and after treatment with IFB, and should have access to appropriate medical care. Patients who develop an infection should be evaluated for appropriate antimicrobial therapy; for serious infections, IFB should be discontinued.

TB (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving IFB. Patients should be evaluated for TB risk

factors and should be tested for latent TB infection prior to initiation of IFB and during therapy.

Treatment of latent TB infection should be initiated prior to therapy with IFB. Treatment of latent TB in patients with a reactive tuberculin test reduces the risk of TB reactivation in patients receiving IFB. Some patients who tested negative for latent TB prior to receiving IFB have developed active TB. Physicians should monitor patients receiving IFB for signs and symptoms of active TB, including patients who tested negative for latent TB infection.

Hepatosplenic T-Cell Lymphomas

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with CD treated with IFB. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatosplenic T-cell lymphomas with IFB have occurred in patients on concomitant treatment with azathioprine or 6-mercaptoprine.

Contraindications¹⁴

IFB at doses greater than 5 mg/kg should not be administered to patients with moderate-to-severe heart failure. In a randomized study evaluating IFB in patients with moderate-to-severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), IFB treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure.

IFB should not be re-administered to patients who have experienced a severe hypersensitivity reaction to IFB. Additionally, IFB should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins.

Warnings¹⁴

Serious infections, including sepsis and pneumonia, have been reported in patients receiving TNF-blocking agents. Some of these infections have been fatal. Although some of the serious infections in patients treated with IFB have occurred in patients receiving concomitant immunosuppressive therapy that, in addition to their underlying disease could predispose them to infections, some patients who were hospitalized or who had a fatal outcome from infection were treated with IFB alone.

IFB should not be given to patients with a clinically important, active infection. Caution should be exercised when one is considering the use of IFB in patients with a chronic infection or a history of recurrent infection. Patients should be monitored for signs and symptoms of infection during or after treatment with IFB. New infections should be closely monitored. If a patient develops a serious infection, IFB therapy

should be discontinued.

Cases of TB, histoplasmosis, coccidioidomycosis, listeriosis, pneumocystosis, and other bacterial, mycobacterial, and fungal infections have been observed in patients receiving IFB.

Patients should be evaluated for TB risk factors and should be tested for latent TB infection. Treatment of latent TB infections should be initiated prior to therapy with IFB. When tuberculin skin testing is performed for latent TB infection, an induration size of 5 mm or greater should be considered positive, even if the patient has been vaccinated previously with bacille Calmette-Guérin (BCG).

Patients receiving IFB should be monitored closely for signs and symptoms of active tuberculosis, particularly since tests for latent tuberculosis infection may be falsely negative. The possibility of undetected latent TB should be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of TB or had close contact with a person with active TB.

All patients treated with IFB should have a thorough history taken prior to initiation of therapy. Some patients who have previously received treatment for latent or active TB have developed active TB while being treated with IFB. Anti-TB therapy should be considered prior to initiation of IFB in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Anti-TB therapy prior to the initiation of IFB should also be considered in patients who have several or highly significant risk factors for TB infection and have a negative test for latent TB. The decision to initiate anti-TB therapy in these patients should be made only after consultation with a physician with expertise in the treatment of TB and taking into account both the risk for latent TB infection and the risks of anti-TB therapy.

For patients who have resided in regions where histoplasmosis or coccidioidomycosis is endemic, the benefits and risks of IFB treatment should be carefully considered before initiation of IFB therapy.

Serious infections were seen in clinical trials with concurrent use of anakinra and another TNF- α -blocking agent, etanercept, with no added clinical benefit compared with etanercept alone. Because of the nature of the ADEs seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF- α -blocking agents. Therefore, the combination of IFB and anakinra is not recommended.

Hepatosplenic T-Cell Lymphoma

Rare postmarketing cases of hepatosplenic T-cell lymphomas have been reported in adolescent and young adult patients with CD treated with IFB. All of these cases have occurred in patients receiving con-

comitant treatment with azathioprine or 6-mercaptopurine.

The clinical course of this disease is very aggressive with a fatal outcome in most patients within two years of diagnosis. The causal relationship of hepatosplenic T-cell lymphoma to IFB therapy remains unclear.

Hepatitis B Virus Reactivation

The use of TNF blockers, including IFB, has been associated with the 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.

Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before TNF-blocker therapy is initiated. Prescribers should exercise caution in prescribing TNF blockers, including IFB, for patients identified as carriers of HBV.

Adequate data are not available on the safety and efficacy of treating patients who are carriers of HBV with antiviral therapy in conjunction with TNF-blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and who require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated.

The safety of resuming TNF-blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF-blocker therapy in this situation and should monitor patients closely.

Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis, have been reported rarely in postmarketing data in patients receiving IFB. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of IFB; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation.

Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., five or more times the ULN) develop, IFB should be discontinued, and a thorough investigation of the

abnormality should be undertaken.

In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving IFB without progression to severe hepatic injury.

Patients with Heart Failure

IFB has been associated with adverse outcomes in patients with heart failure, and it should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized trial evaluating the use of IFB in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been postmarketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking IFB. There have also been rare postmarketing reports of new-onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

If a decision is made to administer IFB to patients with heart failure, they should be closely monitored during therapy, and IFB should be discontinued if new or worsening symptoms of heart failure appear.

Hematological Events

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving IFB. The causal relationship to IFB therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with IFB who have ongoing or a history of significant hematological abnormalities.

All patients should be advised to seek immediate medical attention if they develop signs and symptoms of blood dyscrasias or infection (e.g., persistent fever) while taking IFB. Discontinuation of IFB therapy should be considered in patients who develop significant hematological abnormalities.

Hypersensitivity

IFB has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within two hours of IFB infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial IFB therapy (i.e., as early as after the second dose) and when IFB therapy was re-instituted following an extended period without IFB treatment.

Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, poly-

arthralgias, hand and facial edema, and/or dysphagia. These reactions were associated with a marked increase in antibodies to IFB, loss of detectable serum concentrations of IFB, and possible loss of drug efficacy.

IFB should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids, and/or epinephrine) should be available for immediate use in the event of a reaction.

Neurological Events

IFB and other agents that inhibit TNF have been associated, in rare cases, with optic neuritis, seizure, and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system (CNS) demyelinating disorders, including multiple sclerosis, and CNS manifestations of systemic vasculitis.

Prescribers should exercise caution in considering the use of IFB in patients with pre-existing or recent onset of CNS demyelinating or seizure disorders. Discontinuation of IFB should be considered in patients who develop significant CNS adverse reactions.

Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents, including IFB, more malignancies (excluding lymphoma and non-melanoma skin cancer [NMSC]) have been observed in patients receiving those TNF blockers compared with control patients. During the controlled portions of IFB trials in patients with moderately to severely active RA, CD, psoriatic arthritis (PsA), AS, ulcerative colitis (UC), and plaque psoriasis, malignancies were diagnosed in 14 patients (excluding melanoma and NMSC) among 4,019 IFB-treated patients versus one among 1,597 control patients (at a rate of 0.52/100 patient-years among IFB-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for IFB-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among IFB-treated patients was similar to that expected in the general population, whereas the rate in control patients was lower than expected.

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of IFB clinical trials, five patients developed lymphomas among 5,707 patients treated with IFB (median duration of follow-up, 1.0 year) versus 0 lymphomas in 1,600 control patients (median duration of follow-up, 0.4 year).

In RA patients, two lymphomas were observed, for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for RA, CD, PsA, AS, UC, and plaque psoriasis, five lymphomas were observed, for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population.

Patients with CD, RA, or plaque psoriasis, particularly patients 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 lymphomas, even in the absence of TNF-blocking therapy.

In a clinical trial exploring the use of IFB in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in IFB-treated patients compared with control patients. All patients had a history of heavy smoking. Prescribers should exercise caution when considering the use of IFB in patients with moderate-to-severe COPD.

Psoriasis patients should be monitored for NMSCs, particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for IFB, NMSCs were more common in patients with previous phototherapy.

The potential role of TNF-blocking therapy in the development of malignancies is not known. Rates in clinical trials for IFB cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering IFB treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving IFB.

Precautions and Drug Interactions¹⁴

IFB therapy is associated with several additional drug interactions and adverse events. The following precautions are advised.

Autoimmunity

Treatment with IFB 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 IFB, treatment should be discontinued.

Vaccinations

No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines

not be given concurrently.

It is recommended that all pediatric CD patients be brought up to date with all vaccinations prior to initiating IFB therapy. The interval between vaccination and IFB therapy should be in accordance with current vaccination guidelines.

Information for Patients

Patients developing signs and symptoms of infection should seek medical evaluation immediately. Patients should be provided the REMICADE® Medication Guide and be provided an opportunity to read it and to ask questions prior to each treatment infusion session. Because caution should be exercised in administering IFB to patients with clinically important active infections, it is important that the patient's overall health be assessed at each treatment visit and any questions resulting from the patient's reading of the Medication Guide be discussed.

Drug Interactions

Concurrent administration of etanercept (another TNF- α -blocking agent) and anakinra (an IL-1 antagonist) has been associated with an increased risk of serious infections and an increased risk of neutropenia and no additional benefit compared with these medicinal products alone. Other TNF- α -blocking agents (including IFB) used in combination with anakinra may also result in similar toxicities.

Specific drug-interaction studies, including interactions with MTX, have not been conducted. The majority of patients in RA or CD clinical trials received one or more concomitant medications. In RA, concomitant medications besides MTX were NSAIDs, folic acid, corticosteroids and/or narcotics. Concomitant medications for the treatment of CD were antibiotics, antiviral agents, corticosteroids, 6-MP/AZA and aminosalicylates.

In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as NSAIDs, folic acid, and corticosteroids.

Patients with CD who received immunosuppressants tended to experience fewer infusion reactions than patients receiving no immunosuppressants. Serum IFB concentrations appeared to be unaffected by the baseline use of medications for the treatment of CD, including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

A repeat dose toxicity trial was conducted with mice given cV1q anti-mouse TNF- α to evaluate tumorigenicity. cV1q is an analogous antibody that inhibits the function of TNF- α in mice. Animals were assigned

to one of three dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for six months. The weekly doses of 10 mg/kg and 40 mg/kg are two and eight times, respectively, the human dose of 5 mg/kg for CD.

Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of IFB were observed in the *in vivo* mouse micronucleus test or the *Salmonella–Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether IFB can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity trial with the analogous mouse antibody used in the six-month chronic toxicity trial.

Pregnancy Category B

Because IFB does not cross-react with TNF- α in species other than humans and chimpanzees, animal reproduction trials have not been conducted with IFB. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity trial conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNF- α .

Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacological effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction trials. It is not known whether IFB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. IFB should be given to a pregnant woman only if it is clearly needed.

Nursing Mothers

It is not known whether IFB 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 adverse reactions in nursing infants from IFB, women should not breast-feed their infants while taking IFB. 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

IFB is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active CD who have had an inadequate response to conventional therapy.

IFB has not been studied in children with CD who are younger than six years of age. The longer-term

(greater than one year) safety and effectiveness of IFB in pediatric CD patients have not been established in clinical trials.

The safety and effectiveness of IFB in patients with juvenile rheumatoid arthritis (RA) and pediatric patients with UC and plaque psoriasis have not been established.

Geriatric Use

In RA and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with RA and 75 patients with plaque psoriasis, aged 65 or older who received IFB, compared with younger patients, although the incidence of serious adverse events in patients aged 65 or older was higher in both IFB and control groups compared to younger patients. In CD, UC, AS, and PsA trials, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65.

Because the incidence of infections is higher in the elderly population in general, caution should be used in treating the elderly.

Adverse Reactions^{14*}

Common adverse events seen in clinical trials of IFB include upper respiratory infection, nausea, headache, diarrhea, bronchitis, sinusitis, pharyngitis, cough, abdominal pain, and dyspepsia. This is not a comprehensive list.

Pediatric Crohn's Disease

There were some differences in the adverse reactions observed in the pediatric patients receiving IFB compared with those observed in adults with CD. These differences are discussed in the following paragraphs.

The following adverse events were reported more commonly in 103 randomized pediatric CD patients administered 5 mg/kg of IFB through 54 weeks than in 385 adult CD patients receiving a similar treatment regimen: anemia (11%), blood in the stool (10%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every-eight-week as opposed to every-12-week infusions (74% and 38%, respectively), whereas serious infections were reported for three patients in the every-eight-week and four patients in

the every-12-week maintenance treatment group.

The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for three patients (two in the every-eight-week and one in the every-12-week maintenance treatment groups). Herpes zoster was reported for two patients in the every-eight-week maintenance treatment group.

In Study Peds Crohn's, 18% of randomized patients experienced one or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's, there were no serious infusion reactions, and two patients had non-serious anaphylactoid reactions.

Antibodies to IFB developed in 3% of pediatric patients in Study Peds Crohn's.

Elevations of ALT up to three times the upper limit of normal (ULN) were seen in 18% of pediatric patients in CD clinical trials; 4% had ALT elevations three or more times the ULN, and 1% had elevations five or more times the ULN. (Median follow-up was 53 weeks.)

The most common serious adverse events reported in the postmarketing experience in children were infections (some fatal), including opportunistic infections and tuberculosis, infusion reactions, and hypersensitivity reactions.

Serious adverse events (ADEs) in the postmarketing experience with IFB in the pediatric population have also included malignancies, including hepatosplenic T-cell lymphomas, transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies.

Plaque Psoriasis

During the placebo-controlled portion across the three clinical trials up to Week 16, the proportion of patients who experienced at least one serious ADE (defined as resulting in death, a life-threatening event, an event requiring hospitalization, or persistent or significant disability or incapacity) was 1.7% in the IFB 3-mg/kg group, 3.2% in the placebo group, and 3.9% in the IFB 5-mg/kg group.

Among patients in the two Phase 3 studies, 12.4% of patients receiving IFB 5 mg/kg every 8 weeks through one year of maintenance treatment experienced at least one serious ADE in EXPRESS. In EXPRESS II, 4.1% and 4.7% of patients receiving IFB 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through one year of maintenance treatment experienced at least one serious ADE.

One death resulting from bacterial sepsis occurred 25 days after the second infusion of IFB 5 mg/kg. Serious infections included sepsis and abscesses. In EXPRESS, 2.7% of patients receiving IFB 5 mg/kg every 8 weeks through one year of maintenance treatment experienced at least one serious infection. In

* Discontinuation of treatment with IFB should be considered when significant abnormalities develop.

EXPRESS II, 1.0% and 1.3% of patients receiving IFB 3 mg/kg and 5 mg/kg, respectively, through one year of treatment experienced at least one serious infection. The most common serious infections (requiring hospitalization) were abscesses (skin, throat, and perirectal) reported by five (0.7%) patients in the IFB 5-mg/kg group. Two active cases of TB were reported: six weeks and 34 weeks after starting IFB.

In the placebo-controlled portion of the psoriasis studies, seven of 1,123 patients who received IFB at any dose were diagnosed with at least one NMSC compared with 0 (zero) of 334 patients who received placebo.

In the psoriasis studies, 1% (15 of 1,373) of patients experienced serum sickness or a combination of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of these patients, six required hospitalization because of fever, severe myalgia, arthralgia, swollen joints, and immobility.

Overdosage¹⁴

Single IFB doses of up to 20 mg/kg have been administered without any direct toxic effects. In cases of overdoses, patients should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment should be instituted immediately.

DOSAGE AND ADMINISTRATION¹⁴

Rheumatoid Arthritis. The recommended dose of IFB is 3 mg/kg given as an IV infusion, followed with additional similar doses at two to six weeks after the first infusion, then every eight weeks thereafter. IFB should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every four weeks, bearing in mind that risk of serious infections is increased at higher doses.

Crohn's Disease or Fistulizing Crohn's Disease. The recommended dose of IFB is 5 mg/kg, given as an intravenous induction regimen at zero, two, and six weeks, followed by a maintenance regimen of 5 mg/kg every eight weeks thereafter for the treatment of adults with moderately to severely active CD or fistulizing CD. For adult patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by Week 14 are unlikely to respond with continued dosing, and consideration should be given to discontinue IFB in these patients.

The recommended dose of IFB for children with moderately to severely active CD is 5 mg/kg given as

an IV induction regimen at 0, 2, and six weeks, followed by a maintenance regimen of 5 mg/kg every eight weeks.

Ankylosing Spondylitis. The recommended dose of IFB is 5 mg/kg given as an IV infusion followed with additional similar doses at two and six weeks after the first infusion, then every six weeks thereafter.

Psoriatic Arthritis. The recommended dose of IFB is 5 mg/kg, given as an IV infusion, followed with additional similar doses at two and six weeks after the first infusion, then every eight weeks thereafter. IFB can be used with or without methotrexate.

Ulcerative Colitis. The recommended dose of IFB is 5 mg/kg, given as an induction regimen, at zero, two, and six weeks, followed by a maintenance regimen of 5 mg/kg every eight weeks thereafter, for the treatment of moderately to severely active UC.

Plaque Psoriasis. The recommended dose of IFB is 5 mg/kg given as an intravenous infusion, followed by additional doses at two and six weeks after the first infusion, then every eight weeks thereafter.

Administration Instructions Regarding Infusion Reactions

Adverse effects during administration of IFB have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, GI symptoms, and skin rashes. Anaphylaxis might occur at any time during IFB infusion. Approximately 20% of IFB-treated patients in all clinical trials experienced an infusion reaction compared with 10% of placebo-treated patients. Prior to infusion with IFB, premedication may be administered at the physician's discretion. Premedication could include antihistamines (anti-H₁ ± anti-H₂), acetaminophen, and/or corticosteroids.

During infusion, mild-to-moderate infusion reactions may improve following slowing or suspension of the infusion and, upon resolution of the reaction, re-initiation at a lower infusion rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids. For patients who do not tolerate the infusion following these interventions, IFB should be discontinued.

During or following infusion, patients who have severe infusion-related hypersensitivity reactions should be discontinued from further IFB treatment. The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

Preparation and Administration Instructions

Use Aseptic Technique

IFB vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 ml of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 ml with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/ml and 4 mg/ml. The IFB infusion should begin within three hours of preparation.

1. Calculate the dose and number of IFB vials needed. Each IFB vial contains 100 mg of IFB. Calculate the total number of reconstituted IFB solution required.

2. Reconstitute each IFB vial with 10 ml of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial, and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper, and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. *Do not shake.* Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for five minutes. The solution should be colorless to light yellow or opalescent, and the solution may develop a few translucent particles, as IFB is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.

3. Dilute the total volume of reconstituted IFB solution dose 250 ml with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted IFB from 0.9% Sodium Chloride Injection, USP, 250-ml bottle or bag. Gently mix.

4. The infusion solution must be administered over a period of not less than two hours and must use an infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size, 1.2 µm or less). Any unused portion of the infusion solution should not be stored for reuse.

5. No physical biochemical compatibility studies have been conducted to evaluate the coadministration of IFB with other agents. IFB should not be infused concomitantly in the same IV line with other agents.

6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration, or other foreign particulates are observed, the solution should not be used.

Storage

Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the expiration date. This product contains no preservatives.

How IFB Is Supplied

Infliximab lyophilized concentrate for IV injection is supplied in individually boxed single-use vials in the following strength: NDC 57894-030-01 100 mg of IFB in a 20-ml vial.

Conclusion

Infliximab (IFB, REMICADE[®]) has proved to be efficacious in reducing disease-related signs and symptoms in patients with Crohn's disease (CD) (both adults and children), ankylosing spondylitis (AS), psoriatic arthritis, UC, and plaque psoriasis (PsO), and, in combination with methotrexate (MTX), in patients with rheumatoid arthritis (RA). In addition, IFB is indicated for maintaining clinical remission in adult and pediatric patients with moderately to severely active CD who have had an inadequate response to conventional therapy; for reducing the number of draining enterocutaneous and rectovaginal fistulas; and for maintaining fistula closure in adult patients with fistulizing CD.

IFB is also indicated for inducing and maintaining clinical remission and mucosal healing and eliminating corticosteroid use in patients with moderately to severely active UC who have had an inadequate response to conventional therapy.

In combination with MTX, IFB is also indicated for inhibiting the progression of structural damage and for improving physical function in patients with moderately to severely active RA.

In multiple clinical trials across multiple indications, the benefit–risk profile for IFB is consistently favorable. As with other medications, the benefit–risk ratio for the patient must be considered before health care professionals recommend IFB.

When evaluating IFB for inclusion in a formulary, P&T committees must consider the agent's efficacy in multiple indications, its side effects, and acquisition and monitoring costs. Although IFB has rarely been associated with serious infections according to the aforementioned trials, the possibility should certainly be considered in formulary discussions. Other monitoring parameters may include C-reactive protein, the erythrocyte sedimentation rate, and liver enzyme levels.

Associated costs should also be considered. By reviewing all the facts and making informed decisions about this agent, P&T committees may be able to develop a protocol and categorize patient populations for whom this drug, either as monotherapy or in combination, may be beneficial.

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