Humira (Adalimumab) AHM

Clinical Indications

- Humira (adalimumab) is considered medically necessary any 1 or more of the following
  - Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adults 18 years of age or older with moderately to severely active rheumatoid arthritis. According to the Food and Drug Administration (FDA)-approved product labeling, adalimumab can be used alone or in combination with methotrexate or in combination with nonbiologic disease-modifying anti-rheumatic drugs (DMARDs)
  - Reducing signs and symptoms of active arthritis in adults with moderate to severely active psoriatic arthritis who have had an inadequate response to two or more nonbiologic disease-modifying antirheumatic drugs (DMARDS). According to the FDA-approved product labeling, adalimumab can be used alone or in combination with DMARDs
  - Reducing signs and symptoms of members with active ankylosing spondylitis who have an inadequate response to two or more NSAIDs
  - Members 6 years of age and older with active Crohn's disease despite treatment with either 6-mercaptopurine, azathioprine, or corticosteroids manifested by 1 or more of the following
    - Abdominal pain
    - Arthritis
    - Bleeding
    - Diarheea
    - Internal fistulae
    - Intestinal obstruction
    - Megacolon
    - Perianal disease
    - Spondylitis
    - Weight loss
  - Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (juvenile rheumatoid arthritis) in persons 4 years of age and older
  - Moderate to severe chronic plaque psoriasis for adults aged 18 years and older with who are candidates for systemic therapy or phototherapy when ALL of the following selection criteria are met [A]
- The member has 10% or more body surface area is affected by plaque psoriasis, or member has a Psoriasis Area and Severity Index (PASI) score of 10 or more or 5 percent or more of body surface area if psoriasis involves sensitive areas (hands, feet, face, or genitals).
- Member has failed to adequately respond to or is intolerant to a 3-month trial of 1 or more of the following photo therapies (unless contraindicated):
  - Psoralens (methoxsalen, trioxsalen) with UVA light (PUVA)
  - UVB with coal tar or dithranol
  - UVB (standard or narrow-band)
- For the treatment of active ulcerative colitis in persons who meet 1 or more of the following criteria:
  - Patient is hospitalized with fulminant ulcerative colitis (i.e., persons severe ulcerative colitis who have more than 10 stools per day, continuous bleeding, abdominal pain, and distension, and acute, severe toxic symptoms including fever and anoxia)
  - Patient has moderate to severe active ulcerative colitis and meets ALL of the following criteria:
    - Patient is refractory to or requires continuous immunosuppression with corticosteroids (e.g., methylprednisolone, prednisone) at a dose of prednisone 40 to 60 mg/day (or equivalent) for 30 days for oral therapy or 7 to 10 days for IV therapy
    - Patient is refractory to or has a contraindication to 5-aminosalicylic acid agents (e.g., balsalazide, mesalamine, sulfasalazine)
    - Patient is refractory to or has a contraindication to immunosuppressants (azathioprine and 6-mercaptopurine).
- Current role remains uncertain. Based on review of existing evidence, there are currently no clinical indications for this technology. See Inappropriate Uses for more detailed analysis of the evidence base. Humira (adalimumab) is considered investigational for all other indications, including any of the following conditions, because the safety and effectiveness of adalimumab for these conditions has not been established:
  - Active infections
  - Asthma
  - Cellulitis
  - For use in combination with other tumor necrosis-factor blocking agents [(e.g., etanercept (Enbrel) or infliximab (Remicade) or with anakinra (Kineret)]; or Guttate psoriasis
  - Lupus pernio
  - Osteoarthritis
  - Recurrent pregnancy loss
Evidence Summary

Background

- Humira (adalimumab) (Abbott Laboratories, North Chicago, IL) is a recombinant human IgG1 monoclonal antibody that acts by inhibiting tumor necrosis factor alpha, an inflammatory protein that, when produced in excess, plays a key role in the inflammatory responses of some autoimmune diseases. Adalimumab has been approved by the U.S. Food and Drug Administration (FDA) for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, plaque psoriasis, and juvenile idiopathic arthritis.

- Adalimumab has been approved by the FDA for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis. Adalimumab can be used alone or in combination with methotrexate or other nonbiologic DMARDs. The efficacy and safety of adalimumab were assessed in five randomized, double blind studies in 2869 subjects aged 18 years and older with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. All subjects had at least 6 tender and 9 swollen joints. Humira was administered subcutaneously in combination with methotrexate or as monotherapy or with other disease modifying anti-rheumatic drugs. Two studies involved 815 patients who had failed to respond to DMARDS; one study involved 619 patients who had an inadequate response to methotrexate. One study assessed 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy. One study evaluated 799 patients with moderately to severely active rheumatoid arthritis of less than 3 years duration who were methotrexate naïve. In all five studies, adalimumab showed significantly greater improvement than placebo in standardized indices of disability and health outcomes from baseline to the end of study. One of the five studies also examined the effect adalimumab on inhibition of disease progression, as detected by X-ray results. Subjects treated with adalimumab and methotrexate showed significantly less radiological progression of disease than subjects treated with methotrexate alone. Subjects treated with adalimumab and methotrexate showed significantly less radiological progression of disease than subjects treated with methotrexate alone.
• According to guidelines from the American College of Rheumatology (Saag, et al., 2008), patients with early rheumatology with low or moderate disease activity (in study) were not considered candidates for biologic therapy. The use of anti-TNF agent in combination with methotrexate was recommended if high disease activity was present for less than three months with features of a poor prognosis.

• Adverse events from adalimumab include upper respiratory infection, sinusitis, flu syndrome, nausea, and abdominal pain. Cases of tuberculosis and invasive fungal infections have rarely been observed in patients receiving adalimumab.

• The recommended dose of adalimumab for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous injection.

• The FDA has approved adalimumab for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis. The FDA-approved product labeling for Humira states that adalimumab can be used alone or in combination with methotrexate or with DMARDs. The FDA approval of Humira was based on two multicenter randomized controlled clinical studies evaluating the safety and efficacy of adalimumab compared with placebo in 413 patients with moderate to severely active psoriatic arthritis (greater than 3 swollen and greater than 3 tender joints) who have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDS). In one study (Mease, et al., 2005), 313 patients with moderately to severely active psoriatic arthritis and a history of inadequate response to NSAIDS were randomized to receive 40 mg adalimumab or placebo subcutaneously every other week for 24 weeks. Study participants had the following forms of psoriatic arthritis: 1) distal interphalangeal (DIP) involvement (n = 23); 2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis) (n = 210); 3) arthritis mutilans (n = 1); 4) asymmetric psoriatic arthritis (n = 77); or 5) ankylosing spondylitis-like (n = 2). Patients on methotrexate therapy (158 of 313 patients) at enrollment (stable dose of less than or equal to 30 mg/week for greater than 1 month) could continue methotrexate at the same dose. Study visits were at baseline, weeks 2 and 4, and every 4 weeks thereafter. The primary efficacy end points were the American College of Rheumatology 20% improvement (ACR20) response at week 12 and the change in the modified total Sharp score of structural damage at week 25. Secondary end points were measures of joint disease, disability, and quality of life in all patients, as well as the severity of skin disease in those patients with psoriasis involving at least 3% of body surface area. At week 12, 58% of the adalimumab-treated patients (87 of 151) achieved an ACR20 response, compared with 14% of the placebo-treated patients (23 of 162) (p < 0.001). At week 24, similar ACR20 response rates were maintained and the mean change in the modified total Sharp score was -0.2 in patients receiving adalimumab and 1.0 in those receiving placebo (p < 0.001). Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses
were similar in patients who were or were not receiving concomitant methotrexate therapy at baseline. Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. Among the 69 adalimumab-treated patients evaluated for PASI responses, 59% achieved a 75% PASI improvement response and 42% achieved a 90% PASI improvement response at 24 weeks, compared with 1% of the 69 placebo-treated patients evaluated (p < 0.001). The investigators reported that disability and quality of life measures were also significantly improved with adalimumab treatment compared with placebo.

- Similar results were seen in an additional, 12-week study in 100 patients with moderate to severe psoriatic arthritis who had suboptimal response to DMARD therapy as manifested by greater than or equal to 3 tender joints and greater than or equal to 3 swollen joints at enrollment.

- The manufacturer reported that the rates of adverse events and serious adverse events in clinical trials of adalimumab for psoriatic arthritis submitted for FDA approval were comparable with clinical trials of adalimumab in rheumatoid arthritis. Among patients taking adalimumab, the most common adverse events (those affecting at least 5 percent of patients) were upper respiratory infection, nasopharyngitis, injection site reaction, headache and hypertension. The safety profile of adalimumab in these clinical trials was similar to that observed in the clinical trials of adalimumab for rheumatoid arthritis that were submitted for FDA approval. The FDA-approved product labeling states that the safety and efficacy of adalimumab in pediatric patients has not been established.

- The recommended dose of adalimumab for psoriatic arthritis is 40 mg every-other-week by subcutaneous injection, which is also the usual dose used for adalimumab in the treatment of moderate to severe rheumatoid arthritis.

- Ankylosing spondylitis (AS) is a form of arthritis known as spondyloarthritis, which is a group of closely linked rheumatic diseases that can cause pain in the spine and joints as well as ligaments and tendons. Ankylosing spondylitis is an autoimmune disorder in which tumor necrosis factor (TNF)-alpha has been suggested to play a role in its pathogenesis. A chronic disease, AS primarily affects the spine causing back stiffness and potential deformity over time. Wendling and Toussirot (2004) noted that anti-TNF represents a major therapeutic advancement in the treatment of AS. De Keyser and associates (2006) stated that AS is the prototype disease within the spondyloarthropathies, a group of diseases presenting mainly with spondylitis, pauci-articular peripheral arthritis and enthesiopathy. Non-steroidal anti-inflammatory drugs are the classical cornerstone of medical therapy in these patients; no real DMARD was available, until recently. Tumor necrosis factor-alpha blocking agents (monoclonal antibodies or soluble receptors) are the first representative drugs, of which the indication has recently been expanded to encompass also patients with AS. In a 52-week open-label
study (n = 15, mean age of 40 years with a range of 19 to 55 years), Haibel and colleagues (2006) reported that adalimumab treatment of active AS resulted in a clear improvement in clinical (reduction of spinal symptom) as well as MRI outcome measurements, similar to that observed with other TNF-alpha blocking agents.

- On July 31, 2006, the FDA granted a supplemental indication for adalimumab - for reducing signs and symptoms in patients with active AS. This indication was approved by the European Commission in June 2006. The recommended dosage of adalimumab for AS is 40 mg (subcutaneous injection) every other week. The approval of adalimumab for the treatment of patients with active AS is based on data from the ATLAS (Adalimumab Trial Evaluating Long-Term Efficacy and Safety in AS) trial (n = 315), which was a randomized, placebo-controlled, double-blind, Phase III study conducted in Europe and the United States of patients with AS who had failed to respond to NSAIDs or DMARDS. Results at 12 weeks showed that 58 % of patients receiving adalimumab achieved and sustained a minimum 20 % reduction in pain and inflammation, as measured via the Assessment in AS (ASAS) International Working Group criteria for evaluating function, pain, patient global assessment, and inflammation. At week 24, 42 % of adalimumab-treated patients versus 16 % of those receiving placebo achieved a reduction of 50 % or more in disease activity, as evaluated using a patient-assessed composite index for pain, stiffness, and fatigue (Bath AS Disease Activity Index [BASDAI]). Moreover, approximately 1 of 5 patients achieved partial remission, defined as a value of less than 20 on a 0 to 100 scale in each of the 4 ASAS domains.

- ATLAS also explored the impact of adalimumab on enthesitis, a primary pathology in AS that is characterized by inflammation of the ligaments attachment to the bone. At week 24, the mean change in the enthesitis symptom score as indexed by Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) in patients treated with adalimumab showed significant reduction. MASES is an index that assesses enthesitis in certain locations, such as the rib cage, lower back, and Achilles tendons.

- The British Society for Rheumatology (BSR, 2006) has stated that "there is evidence to support the use of adalimumab as a treatment for adult patients with active AS, who have had an inadequate response to non-steroidal anti-inflammatory drugs and conform to the current BSR guideline for the use of anti-TNF-α drugs in AS." The BSR statement notes that "[w]hilst there have not been any direct comparisons between anti-TNF-α drugs in AS, adalimumab appears to be as effective as any other licensed agents."

- Adalimumab has also been shown in clinical trials to be effective for moderate to severe Crohn's disease. Colombel, et al. (2007) reported on the results of a controlled clinical trial which demonstrated that adalimumab was effective in maintenance of response and remission in patients with moderate to severe Crohn's disease. In this clinical study, patients received open-label induction therapy with adalimumab 80 mg at study initiation followed by 40 mg two weeks later. Four weeks following study initiation, patients who
responded to adalimumab were stratified by response (decrease in Crohn's Disease Activity Index greater than or equal to 70 points from baseline) and randomized to three treatment groups: placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly. Patients were followed for 56 weeks. Coprimary end points were the percentages of randomized responders who achieved clinical remission (Crohn's Disease Activity Index score less than 150) at weeks 26 and 56. The investigators reported that the percentage of randomized responders in remission was significantly greater in the groups receiving adalimumab weekly and every other week compared to the placebo group at week 26 (47%, 40%, and 17%, respectively; p < 0.001) and at week 56 (41%, 36%, and 12%, respectively; p < 0.001). There were no significant differences in efficacy between adalimumab administered weekly and every other week. The investigators noted that adalimumab was well tolerated; more patients receiving placebo discontinued treatment because of an adverse event (13.4%) than those receiving adalimumab (4.7% and 6.9% in the adalimumab weekly and every other week groups, respectively). The investigators concluded that, among patients who responded to adalimumab, both weekly and every other week adalimumab was significantly more effective than placebo in maintaining remission in moderate to severe Crohn's disease through 56 weeks.

- Hanauer, et al. (2006) reported that adalimumab was shown in a controlled clinical trial to be superior to placebo for induction of remission in patients with moderate to severe Crohn's disease. A total of 299 patients with moderate to severe Crohn's disease naive to anti-tumor necrosis factor (TNF) therapy were randomized to receive subcutaneous injections at study initiation and two weeks later with adalimumab 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg or placebo. The primary endpoint was demonstration of a significant difference in the rates of remission (defined as a Crohn's Disease Activity Index score <150 points) at four weeks after study initiation among the 80 mg/40 mg, 160 mg/80 mg, and placebo groups. The investigators found that the rates of remission at the fourth week in the adalimumab 40 mg/20 mg, 80 mg/40 mg, and 160 mg/80 mg groups were 18% (p = 0.36), 24% (p = 0.06), and 36% (p = 0.001), respectively, and 12% in the placebo group. The investigators reported that adalimumab was well tolerated, noting that adverse events occurred at similar frequencies in all four treatment groups except injection site reactions, which were more common in adalimumab-treated patients. The investigators concluded that adalimumab was superior to placebo for induction of remission in patients with moderate to severe Crohn's disease naive to anti-TNF therapy. The investigators stated that the optimal induction dosing regimen for adalimumab in this study was 160 mg at initiation of therapy followed by 80 mg two weeks later.

- Colombel et al (2009) compared outcomes of induction dosing followed by continuous adalimumab treatment with those of induction dosing with re-initiation of adalimumab (in the event of clinical deterioration) for patients with moderate-to-severe Crohn's disease who participated in the Crohn's Trial of the Fully Human Antibody Adalimumab...
for Remission Maintenance (CHARM). In the CHARM trial, all patients received open-label induction therapy with adalimumab 80 mg and 40 mg at weeks 0 and 2, respectively. In total, 778 patients were randomized at week 4 to one of three groups: (i) placebo after initial induction doses (followed by re-initiation of adalimumab therapy); (ii) continuous maintenance treatment with adalimumab 40 mg every other week (e.o.w.); and (iii) continuous maintenance treatment with adalimumab 40 mg every week. At/after week 12, patients receiving placebo with flare or non-response could re-initiate open-label adalimumab 40 mg e.o.w., and patients receiving continuous blinded adalimumab therapy could switch to open-label 40 mg e.o.w. Patients in all groups could switch to weekly therapy with continued flare/non-response. In the previously published primary analysis, results for only those patients who had responded at week 4 (decrease in Crohn's Disease Activity Index (CDAI) of greater than or equal to 70 points, referred to as "randomized responders") and remained on blinded therapy were analyzed. In this analysis, data from all randomized patients were analyzed based on original randomized treatment using an intention-to-treat analysis, regardless of whether they subsequently switched to open-label therapy. Disease activity, clinical remission, number of flares, Inflammatory Bowel Disease Questionnaire (IBDQ) score, number of Crohn's disease-related surgeries, and hospitalization incidence were compared between the continuous and induction only/re-initiation adalimumab groups. Results for all outcome measures were superior for both continuous groups compared with the induction only/re-initiation group. On the basis of median CDAI and IBDQ results, patients in both continuous treatment groups achieved statistically significantly greater improvements versus the induction only/re-initiation group (p < 0.05). At week 56, a significantly greater percentage of patients who had received continuous adalimumab (51 % for e.o.w. and 49 % for weekly) were in clinical remission versus the induction only/re-initiation group (38 %, p < 0.05). Continuous adalimumab therapy was also associated with fewer flares and fewer Crohn's disease-related surgeries (p < 0.05). Patients in both continuous adalimumab groups had significantly lower risks of Crohn's disease-related and all-cause hospitalizations than did patients in the induction only/re-initiation group (p < 0.05). The authors concluded that for patients with active Crohn's disease, continuous treatment with adalimumab was more effective than a strategy of induction dosing followed by re-initiation of adalimumab with clinical deterioration for maintenance of clinical remission, improved quality-of-life outcomes, reduced flares, and a decrease in number of surgeries and risk of hospitalization.

- Adalimumab has been approved by the FDA for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients four years of age and older. In the United States, JIA is commonly referred to as juvenile rheumatoid arthritis (JRA). JIA is the most common chronic rheumatic disease in children with onset before age 16. Typical symptoms include stiffness when awakening,
limping, and joint swelling. Any joint can be affected and inflammation may limit the mobility of the affected joints. Polyarticular JIA is a form of arthritis affecting 5 or more joints, usually in a symmetrical fashion. While it was once believed that most children eventually outgrow JIA, it is now known that between 25 and 70 percent of children with JIA will still have active disease into adulthood.

- The approval of adalimumab for JIA was based on the results of a 48-week study and a subsequent open-label extension evaluating the efficacy and safety of adalimumab in children with JIA. The 48-week Phase III study included 171 children (four to 17 years of age) with polyarticular JIA. In the first part of this study, two groups of children – those taking methotrexate (MTX) and those not taking MTX – received open-label adalimumab (up to a maximum of 40 mg) every other week for 16 weeks. Patient responses were measured using the American College of Rheumatology Pediatric (ACR Pedi) 30 score, which represents a 30% or greater improvement in JIA signs and symptoms. Children who showed a positive clinical response (n= 133) entered the second part of the study and were randomized to receive adalimumab or placebo for an additional 32 weeks or until disease flare. A flare was defined as a worsening of 30% or more in at least three of the six ACR Pedi response variables, a minimum of two active joints, and no more than one indicator improving by 30%. In the second part of this study, significantly fewer children receiving adalimumab demonstrated disease flare compared to children on placebo, both without MTX (43% versus 71%) and with MTX (37% versus 65%). Additionally, more children treated with adalimumab continued to show ACR Pedi 30/50/70 responses at week 48 compared to placebo. At the conclusion of the 48-week study or at the time of disease flare during the double-blind phase, children could enter the open-label extension period. Efficacy and safety were assessed at routine intervals throughout the study. ACR Pedi responses were maintained for up to two years in children who received adalimumab throughout the study. Upon initiation of treatment with adalimumab, the most common adverse reactions that occurred were injection site pain and injection site reaction (19% and 16%, respectively). In general, adverse reactions in children were similar in frequency and type to those seen in adult patients. Severe adverse reactions reported in the clinical trial in JIA included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia and appendicitis. Serious infections were observed in 4% of children within approximately two years of initiation of treatment with adalimumab and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster. Recommended dosing in JIA is based upon weight. For children 15 kg (33 lbs) to less than 30 kg (< 66 lbs), recommended dose is 20 mg by injection every other week. For children 30 kg (66 lbs) and greater, recommended dose is 40 mg by injection every other week.

- Adalimumab has been approved by the FDA for the treatment for adults with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy,
and when other systemic therapies are medically less appropriate. According to the FDA-approved labeling, adalimumab should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. Chronic plaque psoriasis is an autoimmune disease characterized by inflamed, scaly skin lesions known as plaques, which may crack and bleed. While psoriasis can occur in people of all ages, it typically appears in patients between the ages of 15 and 35 years. Approximately 25% of persons with chronic plaque psoriasis exhibit moderate to severe disease. Up to 30 percent of psoriasis patients develop psoriatic arthritis. Treatment may include topical agents, phototherapy or oral or injectable medications.

- The FDA approval of adalimumab for chronic plaque psoriasis was based on two pivotal trials, REVEAL and CHAMPION, showing that approximately 3 out of 4 patients achieved 75% clearance or better at week 16 of treatment versus placebo. Both studies evaluated the efficacy and safety of HUMIRA in clearing skin in moderate to severe adult plaque psoriasis patients versus placebo. In addition, CHAMPION compared a biologic medication to methotrexate, a standard systemic treatment for psoriasis. In each trial, reduction in disease activity was determined by the Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA). In REVEAL, a 52-week trial, the short-term and sustained clinical efficacy and safety of adalimumab were evaluated in 1212 patients with moderate to severe chronic plaque psoriasis.

- Patients experienced a significant reduction in the signs and symptoms of their disease at 16 weeks when treated with adalimumab. Specifically, 71% of patients receiving adalimumab achieved PASI 75 compared to 7% of patients receiving placebo at week 16. At week 16, 62% of adalimumab-treated patients achieved a PGA score of clear or minimal compared to 4% of placebo-treated patients. In CHAMPION, a 16-week study evaluating 271 psoriasis patients, adalimumab-treated patients experienced a significant reduction in the signs and symptoms of their disease compared with methotrexate or placebo-treated patients. Seventy-eight percent of patients treated with adalimumab (n=99) achieved a PASI 75 response, compared to 19% of patients treated with placebo (n= 48). Seventy-one percent of patients treated with adalimumab achieved a PGA score of clear or minimal at 16 weeks of treatment, compared with 10% of placebo-treated patients. The safety profile of adalimumab in the plaque psoriasis clinical trials was reported to be similar to that seen in adalimumab clinical trials for rheumatoid arthritis. The most commonly reported adverse events in adalimumab psoriasis trials were upper respiratory tract infection, nasopharyngitis (inflammation of the nose and pharynx), headache, sinusitis and arthralgia. In clinical studies of plaque psoriasis, patients are treated with an initial 80 mg dose of adalimumab (two 40 mg injections) followed by one adalimumab injection (40 mg) one week later. After that, a maintenance dose of 40 mg was administered every other week.
• Adalimumab has not been proven to be effective for ulcerative colitis. In an open-label study, Peyrin-Biroulet et al (2007) assessed the effectiveness of adalimumab induction therapy in patients with ulcerative colitis who previously responded to infliximab and then lost response or became intolerant. A total of 10 patients with ulcerative colitis were enrolled in a 4-week trial. Patients received a loading dose of 160 mg adalimumab at week 0 followed by 80 mg at week 2. The primary outcome measure was clinical improvement at week 4, as defined by a decrease in clinical activity index (CAI) of more than 4. Four of 10 patients (40 %) benefited from subsequent adalimumab therapy; 1 patient achieved remission (CAI less than 4) and 3 had clinical improvement at week 4. 6 patients had no response (60 %); 2 of 6 (33.3 %) subsequently underwent colectomy. This was accompanied by a decrease in median CRP concentration from 16.8 mg/ml at baseline to 3.85 mg/ml at week 4, excluding 2 patients who underwent colectomy after two infusions of adalimumab. Among the 6 patients with severe colitis (CAI greater than 12) at baseline, none achieved remission and only 1 patient had clinical improvement at week 4. The authors concluded that the small advantage of adalimumab in patients with mild to moderate ulcerative colitis and lost response or intolerance to infliximab needs to be confirmed in randomized, double-blind, placebo-controlled trials. Furthermore, in a Cochrane review on TNF-alpha blocking agents for induction of remission in ulcerative colitis, Lawson et al (2006) did not mention the use of adalimumab.

• In a pilot study (n = 12), Magnano et al (2007) examined if adalimumab can safely improve symptoms of erosive/inflammatory osteoarthritis (EOA). Patients greater than 45 years of age with EOA of the hands defined by greater than or equal to 2 tender and greater than or equal to 2 swollen joints (distal inter-phalangeal, proximal inter-phalangeal, first carpo-metacarpal) despite non-steroidal anti-inflammatory drug therapy were eligible. Patients were excluded for autoimmune arthritis, recent disease modifying anti-rheumatic drug use, prior use of anti-TNF therapy, infection, malignancy, or poorly controlled medical conditions. All patients received adalimumab 40 mg every other week for 12 weeks. Safety was assessed 4 weeks after the final dose. Primary endpoints included safety and ACR response. Patients were predominantly female with a mean age of 60 years and 12 years of arthritis. All subjects completed the study and safety follow-up. Adverse events were mild without necessitating discontinuation of study drug. After 12 weeks, there was a statistically significant improvement in the number of swollen joints compared to baseline (p < 0.01). One patient achieved an ACR20 response and 42 % achieved an OMERACT-OARSI response. Although these investigators detected no statistically significant improvement in the number of tender joints, grip strength, disability, pain, or global disease assessments, trends suggested modest improvement in all efficacy measures. The authors concluded that the findings of this small open-label study of patients with EOA demonstrated that adalimumab was well-tolerated. Treatment with adalimumab for 3 months did not significantly improve the signs and symptoms of
EOA and most patients did not achieve an ACR20. Trends suggested improvement and individual patients had some benefit. Factors limiting interpretation of this study include the lack of a control group, outcomes chosen, number of patients treated, and the duration of treatment.

- Cutaneous sarcoidosis may be a chronic disease with important morbidity requiring aggressive therapy. The effectiveness of different anti-TNF-α treatments in refractory cutaneous and systemic sarcoidosis has been reported previously. Thielen et al (2009) reported the first patient with chronic cutaneous sarcoidosis who responded to dose escalation of anti-TNF-α agents that have been ineffective at the standard dosage, illustrating that the optimal dosing regimen has still to be defined for this indication before considering difficult-to-treat patients as non-responders. This case report also illustrated that the fusion protein etanercept, even used at a high dosage, may be less effective for the treatment of cutaneous sarcoidosis than the monoclonal antibodies infliximab and adalimumab.

- Patel (2009) stated that sarcoidosis is an inflammatory disorder characterized by the presence of non-caseating granulomas in affected organs. The presence of CD4-positive T lymphocytes and macrophages in affected organs suggests an ongoing immune response. Systemic corticosteroids remain the mainstay of treatment, but therapy is often limited by adverse effects. This is the first report of the use of adalimumab in a patient with systemic sarcoidosis with bone marrow involvement. The patient was a 42-year-old African-American man with a medical history significant for hypertension and diabetes mellitus presented with anemia and thrombocytopenia of 2-month duration. He underwent physical examination, bone marrow aspiration and biopsy, chest X-ray, acid-fast bacilli stain, computed tomography with contrast, and additional laboratory tests; and was diagnosed with systemic sarcoidosis with splenomegaly and bone marrow involvement. Drug therapy included prednisone, which had to be discontinued owing to adverse effects, and adalimumab. The author concluded that this is the first report describing the use of adalimumab in a patient with systemic sarcoidosis with bone marrow involvement. Tumor necrosis factor antagonism with adalimumab was effective and well-tolerated in this patient and may be considered as a treatment option for similar cases.

- Antoniu (2010) noted that sarcoidosis is a granulomatous disease with various organ manifestations in which TNF-α has been demonstrated to play a major pathogenic role. Conventional therapies are not always able to minimize TNF-α-driven inflammation and other approaches should be used. The author reviewed TNF-α roles in sarcoid inflammation and granuloma formation based on the literature published in the last 20 years and the therapies able to target it specifically or non-specifically in sarcoidosis were discussed. In some subsets of sarcoidosis with more rapid progression and/or therapeutic
refractoriness TNF-α plays a more prominent role in disease pathogenesis, and its blockade might represent an appropriate therapeutic approach.

- In a multi-center, double-blind, randomized, controlled trial, Genevay and colleagues (2010) evaluated the effectiveness of adalimumab in patients with radicular pain due to lumbar disc herniation. Patients with acute (less than 12 weeks) and severe (Oswestry Disability index greater than 50) radicular leg pain and imaging-confirmed lumbar disc herniation were randomized to receive as adjuvant therapy either 2 subcutaneous injections of adalimumab (40 mg) at 7-day interval or matching placebo. The primary outcome was leg pain, which was recorded every day for 10 days and at 6 weeks and 6 months based on a visual analog scale (0 to 100). Of the 265 patients screened, 61 were enrolled (adalimumab = 31) and 4 were lost to follow-up. Over time, the evolution of leg pain was more favorable in the adalimumab group than in the placebo group (p < 0.001). However, the effect size was relatively small and at last follow-up the difference was 13.8 (95 % confidence interval; -11.5 to 39.0). In the adalimumab group, twice as many patients fulfilled the criteria for "responders" and for "low residual disease impact" (p < 0.05) and fewer surgical discectomies were performed (6 versus 13, p = 0.04). The authors concluded that the addition of a short course of adalimumab to the treatment regimen of patients suffering from acute and severe sciatica resulted in a small decrease in leg pain and in significantly fewer surgical procedures. Limitations of this study include small sample sizes, inability to determine the sufficient dose and best route of administration for TNF-α inhibitors in radiculopathy because of disk herniation, or to identify subgroups of patients most likely to respond to this treatment. More studies are needed to ascertain the adequate dose and the best route of administration of TNF-α inhibitors, elucidating the effective therapeutic role of TNF-α inhibitors in this disease and determining the dosage, times and route of administration, as well as evaluating the possible occurrence of harmful events, as serious infections or adverse cardiovascular events, as seen in patients with rheumatoid arthritis treated with biological drugs.

- The FDA-approved product labeling for Humira includes a black box warning about the risk of serious infections with adalimumab. The labeling states that patients treated with Humira are at increased risk of developing serious infections that may lead to hospitalizations or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. The labeling states that Humira should be discontinued if a patient develops a serious infection or sepsis.

- The labeling states that tuberculosis (TB), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving adalimumab. The labeling notes that some of these infections have been fatal.

- Active tuberculosis including reactivation of latent tuberculosis has been reported in patients taking Humira. Patients with tuberculosis have frequently presented with
disseminated or extrapulmonary disease. Anti-TB treatment of patients with latent TB infection reduces the risk of reactivation in patients receiving adalimumab. However, active TB has developed in patients receiving adalimumab whose screening for latent TB infection was negative. The labeling recommends that patients should be evaluated for TB risk factors and be tested for latent TB prior to initiating adalimumab and during therapy. According to the product labeling, when TB skin testing is performed, an induration size of 5 mm or greater should be considered positive, even if the patient was previously vaccinated with Bacille Calmette-Guerin (BCG). Treatment of latent TB should be initiated prior to therapy with adalimumab. The labeling recommends that physicians should monitor patients receiving adalimumab for signs and symptoms of active TB, including patients who tested negative for latent TB.

- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis, have been reported in patients taking Humira. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. The labeling states that empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.

- Bacterial, viral and other infections due to opportunistic infections have been reported. The labeling recommends that the risks and benefits of treatment with Humira should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Humira, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

- The labeling states that cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Humira has not been formally studied in patients with CHF; however, in clinical studies in CHF of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. The labeling recommends to exercise caution when using Humira in patients who have heart failure, and to monitor patients with heart failure carefully.

- Fiorino et al (2011) summarized available data on the safety and effectiveness profile of adalimumab in patients with UC. The authors concluded that adalimumab may be effective and well-tolerated in UC. Moreover, they stated that its effectiveness in maintaining clinical remission needs to be confirmed in a randomized controlled trial.

- Tato and colleagues (2005) noted that treatment of patients with Takayasu's arteritis remains a demanding challenge to clinicians. In many patients, the course of the disease is characterized by frequent relapses and disease progression under conventional treatment with glucocorticoids and cytotoxic drugs. These researchers presented the case
of a young woman with severe cerebrovascular and aortic involvement, who experienced disease progression in spite of more than 2 years of treatment with high doses of prednisone, methotrexate and cyclophosphamide. In this patient, treatment with adalimumab achieved clinical remission and allowed tapering of prednisone within a few months. The present case, as well as previous reports on the use of infliximab in giant cell and Takayasu's arteries, suggested that TNFalpha-blockade may be a new, promising treatment for glucocorticoid-refractory large-vessel vasculitis.

- Ramos-Casals et al (2008) stated that in 2006, the Study Group on Autoimmune Diseases (GEAS) of the Spanish Society of Internal Medicine created the BIOGEAS project, a multi-center study devoted to collecting data on the use of biological agents in adult patients with systemic autoimmune diseases (SAD). The information source is a periodic surveillance of reported cases by a MEDLINE search (last update before this writing: December 31, 2007). The analysis included a total of 19 SAD and 6 biological agents. By December 31, 2007, the Registry included 1,370 patients with SAD who had been treated with biological agents (562 received infliximab, 463 rituximab, 285 etanercept, 42 anakinra, and 18 adalimumab).

- Systemic autoimmune diseases included Sjogren syndrome (SS; 215 cases), Wegener granulomatosis (261 cases), sarcoidosis (219 cases), systemic lupus erythematosus (SLE; 172 cases), Behcet disease (173 cases), adult-onset Still disease (118 cases), cryoglobulinemia (88 cases), and other diseases (80 cases). The higher rate of therapeutic response was found for the use of rituximab in patients with SLE (90 %), SS (91 %), anti-phospholipid syndrome (92 %), and cryoglobulinemia (87 %); infliximab in sarcoidosis (99 %), adult-onset Still disease (90 %), and polychondritis (86 %); and etanercept in Behcet disease (96 %). Results from controlled trials showed lack of efficacy for the use of infliximab in SS and etanercept in SS, Wegener granulomatosis, and sarcoidosis. In addition, an excess of side effects (greater than 50 % of reported cases) was observed for the use of infliximab in inflammatory myopathies and sarcoidosis, and for the use of etanercept in polymyositis.

- Sufficient data are not yet available to evaluate fully the safety and effectiveness of adalimumab and anakinra in patients with SAD. The authors concluded that current scientific evidence on the use of biological therapies in patients with SAD is mainly based on uncontrolled, observational data. The best results have been observed in the use of rituximab for SS, SLE, and cryoglobulinemia; infliximab for sarcoidosis and adult-onset Still disease; and etanercept for Behcet disease. Lack of efficacy was demonstrated for infliximab and etanercept in SS, for etanercept in Wegener granulomatosis and sarcoidosis, and for TNF in SS. They stated that future controlled trials are needed to confirm the potential use of biological therapies in patients with SAD.

- Androudi et al (2010) evaluated the safety and effectiveness of intra-vitreal adalimumab injections on refractory cystoid macular edema (CME) secondary to non-infectious
uveitis. A total of 8 consecutive patients with controlled uveitis and chronic, refractory CME who had failed steroid treatment were included in this study. Intra-vitreal adalimumab injections were given monthly for 3 months. Main outcome measure was mean change in central retinal thickness (CRT) on optical coherence tomography (OCT); secondary objective was the mean change in best-corrected visual acuity (BCVA). Five of the 8 patients completed the 6-month follow-up. For all 5 patients, the changes in BCVA from baseline to 3 months were not statistically significant (p = 0.070). Similarly, the change in BCVA from baseline to 6 months was not statistically significant (p = 1.0). The mean CRT at baseline was 692 microm.

- The changes from baseline to 3 months were not statistically significant (p = 0.466); the changes from baseline to 6 months were also not statistically significant (p = 0.808). These researchers did not observe any ocular or systemic adverse effects. The authors concluded that intra-vitreal adalimumab showed no efficacy in improving BCVA or reducing CRT in patients with chronic uveitic macular edema. Furthermore, Neri et al (2011) stated that adalimumab is a promising drug for the treatment of uveitis, although further studies are needed on its application in uveitis.

- Hyams et al (2012) evaluated the safety and effectiveness of adalimumab double-blind maintenance dosing regimens following open-label induction for pediatric patients with moderate-to-severe Crohn's disease (CD). These investigators studied 192 patients with Pediatric Crohn's Disease Activity Index (PCDAI) scores greater than 30 for whom conventional treatment was unsuccessful. Patients received open-label induction therapy with subcutaneous adalimumab at weeks 0 and 2 (160 mg and 80 mg, or 80 mg and 40 mg, for body weight [BW] greater than or equal to 40 kg or less than 40kg). At week 4, 188 patients were assigned to groups based on achievement of clinical response (defined as PCDAI decrease less than or equal to 15 points from baseline, 155/188 [82.4 %]) and prior exposure to infliximab (82/188, 43.6 %).

- Groups were given double-blind maintenance therapy with adalimumab at high (40 mg or 20 mg for BW greater than or equal to 40 kg or less than 40 kg; n = 93) or low doses (20 mg or 10 mg for BW greater than or equal to 40 kg or less than 40 kg; n = 95), every other week for 48 weeks. Clinical remission (PCDAI less than or equal to 10) at week 26 (the primary endpoint) was compared between groups using the Cochran-Mantel-Haenszel test, adjusting for strata, with non-responder imputation. Adverse events were monitored to evaluate safety; 152/188 patients (80.9 %) completed all 26 weeks of the study. At week 26, 63 patients (33.5 %) were in clinical remission, with no significant difference between high- and low-dose groups (36/93, 38.7 % versus 27/95, 28.4 %; p = 0.075).

- No new safety signals were detected. The authors concluded that adalimumab induced and maintained clinical remission of children with CD, with a safety profile comparable to that of adult patients with CD. More children that received high than low dose were in...
remission at week 26, but the difference between dose groups was not statistically significant.

- In a prospective case series, Diaz-Llopis et al (2012) evaluated adalimumab therapy in refractory uveitis. A total of 131 patients with refractory uveitis and intolerance or failure to respond to prednisone and at least 1 other systemic immunosuppressive drug participated in this study. Patients received a 40-mg adalimumab subcutaneous injection every other week for 6 months. The associated immunosuppressants were tapered after administering 3 adalimumab injections (week 6). Main outcome measure were degree of anterior and posterior chamber inflammation (Standardization of Uveitis Nomenclature Working Group criteria), immunosuppression load (as defined by Nussenblatt et al), VA (logarithm of the minimal angle of resolution [logMAR]), and macular thickness (OCT). There were 61 men and 70 women (mean age of 27.3 years). The most common causes were juvenile idiopathic arthritis in 39 patients, pars planitis in 16 patients, and Behcet's disease in 13 patients.

- Twenty-seven patients had uveitis of idiopathic origin. Inflammation in the anterior chamber was present in 82% of patients and in the vitreous cavity in 59% of patients. Anterior chamber inflammation and vitreous inflammation decreased significantly ($p < 0.001$) from a mean of 1.51 and 1.03 at baseline to 0.25 and 0.14, respectively, at 6 months. Macular thickness was 296 (102) μ at baseline versus 240 (36) μ at the 6-month visit ($p < 0.001$). Visual acuity improved by -0.3 logMAR in 32 of 150 eyes (21.3%) and worsened by +0.3 logMAR (-15 letters) in 5 eyes (3.3%). The dose of corticosteroids also decreased from 0.74 (3.50) to 0.20 (0.57) mg/kg/day ($p < 0.001$). Cystoid macular edema, which was present in 40 eyes at baseline, showed complete resolution in 28 eyes at 6 months. The mean suppression load decreased significantly (8.81 [5.05] versus 5.40 [4.43]; $p < 0.001$).

- Six months after the initiation of the study, 111 patients (85%) were able to reduce at least 50% of their baseline immunosuppression load. Only 9 patients (6.9%) had severe relapses during the 6 months of follow-up. The authors concluded that adalimumab seems to be well-tolerated and helpful in decreasing inflammatory activity in refractory uveitis and may reduce steroid requirement. Moreover, they stated that further controlled studies of adalimumab for uveitis are needed.

- On September 28, 2012, the FDA approved adalimumab for the treatment of moderate-to-severe ulcerative colitis in adults. The approval was based on findings of 2 clinical studies showing the safety and effectiveness of adalimumab for ulcerative colitis. A total of 908 patients who had never been treated with a TNF-blocker, or who lost response to or were intolerant to TNF-blockers participated in the studies. All patients enrolled in the studies had a Mayo score of 6 to 12 and an endoscopy subscore of 2 to 3. Patients were randomly assigned to take adalimumab or a placebo. The studies were designed to measure the percentage of patients whose Mayo score decreased to 2 or less with no
individual subscore of more than 1 after 8 weeks of treatment. Patients who obtained such reductions in the Mayo score were determined to have achieved clinical remission.

- Results from both studies showed 16.5% to 18.5% of patients treated with adalimumab achieved clinical remission compared with 9.2% to 9.3% of patients receiving placebo. Additionally, in the 2nd study, 8.5% of patients treated with adalimumab sustained clinical remission compared with 4.1% of patients treated with placebo. The effectiveness of adalimumab has not been established in patients with ulcerative colitis who have lost response to or were intolerant to TNF blockers.

- The FDA-approved dosing regimen for adalimumab for ulcerative colitis begins with an initial dose of 160 milligrams, a 2nd dose 2 weeks later of 80 mg, and a maintenance dose of 40 mg every other week, thereafter. The drug should only continue to be used in patients who have shown evidence of clinical remission by 8 weeks of therapy.

- Adalimumab has been used successfully in children and adolescents with Crohn's disease who do not respond or develop infusion reactions to infliximab. A randomized controlled trial (Hyams, et al., 2012) comparing two doses of adalimumab in 188 patients with refractory moderate-to-severe pediatric Crohn's disease found comparable rates of remission with the two dosing regimens, occurring in about one-third of subjects at six months. In a retrospective series of 115 persons with refractory pediatric Crohn's disease treated with adalimumab (Rosh, et al., 2009), 70 percent had a clinical response at one year.

- In September 2014, the FDA expanded approval of adalimumab for reducing signs and symptoms, and achieving and maintaining clinical remission, in pediatric Crohn's disease patients 6 years of age and older when certain other treatments have not worked well enough (Abbvie, 2014). The FDA approval of adalimumab for pediatric Crohn's was supported by the Phase 3 IMAGINE-1 trial, a multi-center, randomized, double blind trial, that evaluated multiple dosing strategies of adalimumab to induce and maintain clinical remission in pediatric patients 6 to 17 years of age with moderately to severely active Crohn's disease for whom certain other treatments have not worked well enough (Hyams, et al., 2012).

- Hyams et al (2012) evaluated the safety and effectiveness of adalimumab double-blind maintenance dosing regimens following open-label induction for pediatric patients with moderate-to-severe Crohn's disease (CD). These investigators studied 192 patients with Pediatric Crohn's Disease Activity Index (PCDAI) scores greater than 30 for whom conventional treatment was unsuccessful. Patients received open-label induction therapy with subcutaneous adalimumab at weeks 0 and 2 (160 mg and 80 mg, or 80 mg and 40 mg, for body weight [BW] greater than or equal to 40 kg or less than 40kg). At week 4, 188 patients were assigned to groups based on achievement of clinical response (defined as PCDAI decrease less than or equal to 15 points from baseline, 155/188 [82.4%]) and prior exposure to infliximab (82/188, 43.6%). Groups were given double-blind maintenance therapy with adalimumab at high (40 mg or 20 mg for BW greater than or equal to 40 kg or less than 40 kg; n = 93) or low doses (20 mg or 10 mg for BW greater
than or equal to 40 kg or less than 40 kg; n = 95), every other week for 48 weeks. Clinical remission (PCDAI less than or equal to 10) at week 26 (the primary endpoint) was compared between groups using the Cochran-Mantel-Haenszel test, adjusting for strata, with non-responder imputation. Adverse events were monitored to evaluate safety; 152/188 patients (80.9 %) completed all 26 weeks of the study. At week 26, 63 patients (33.5 %) were in clinical remission, with no significant difference between high- and low-dose groups (36/93, 38.7 % versus 27/95, 28.4 %; p = 0.075). No new safety signals were detected. The authors concluded that adalimumab induced and maintained clinical remission of children with CD, with a safety profile comparable to that of adult patients with CD. More children that received high than low dose were in remission at week 26, but the difference between dose groups was not statistically significant.

- In a case-cohort interventional study, Sen et al (2012) examined the use of adalimumab in the treatment of refractory non-infectious childhood chronic uveitis. This study was performed on patients with uveitis, who were treated with adalimumab after failure of treatment with a combination of corticosteroids and another immunosuppressant drug. Main outcome measures were (i) stability of vision, (ii) stability of inflammation and (iii) reduction of immunosuppressive load. Adverse events and reasons for stopping adalimumab were noted. A total of 17 patients from a single regional center were included in the study; 9 patients had previously received an anti-TNF agent, and because of inefficacy, all were changed to adalimumab. At 12 months, fewer patients had visual acuity worse than LogMAR 0.4 (18 % versus 32 % at baseline). Using standardized uveitis nomenclature criteria, at 3 months, 50 % of the patients eyes (n = 32) had improved, 16 % had stable inflammation and 3 % had worsened, whereas 31 % were maintained with no anterior chamber cells. Six patients required courses of oral steroids for uveitis. Seven patients received intra- or peri-ocular injections of steroids. Adalimumab treatment was interrupted in 1 patient because of varicella zoster infection. It was stopped in 3 patients; 7 (41 %) patients reported injection site reactions. The authors concluded that in this group of children with refractory uveitis, use of adalimumab was associated with improvement in visual acuity and improving or stable ocular inflammation. However, it did not completely obviate the need for systemic or peri-ocular steroid treatment. They stated that prospective randomized controlled trials are needed to help determine which subset of patients may benefit from adalimumab and the duration of treatment.

- Bravo-Ljubetic et al (2013) reported the results of adalimumab therapy in a cohort of children with refractory non-infectious uveitis. The medical records of patients diagnosed with uveitis and treated with bi-weekly adalimumab injections for a period of at least 3 months at the University Hospital of La Paz from 2007 to 2012 were retrospectively reviewed. Improvement in inflammatory activity was graded according to grading schema of the Standardization of Uveitis Nomenclature Working Group. A total of 15 patients participated in the study (12 girls; mean patient age of 12 years). Diagnoses were JIA in 10 patients, idiopathic uveitis in 4, and familial juvenile systemic granulomatosis or Blau syndrome in 1. Mean follow-up was 32 months (median of 36; range of 15 to 58 months). Improvement in inflammatory activity was initially observed in 12 (86 %) of 14 children, with a mean time to achieve response of 6 weeks (median of 4; range of 1 to
18). Treatment was effective in 9 patients (60 %), mildly effective in 2 (13 %), ineffective in 2 (13 %), and resulted in worsening in 2 (13 %). In the JIA patients, response was effective in 6 cases (60 %), mildly effective in 2 (20 %), and ineffective in 2 (20 %). Adalimumab therapy was discontinued in 4 patients. The authors concluded that adalimumab was effective in most patients in the initial control of acute inflammatory activity in children with refractory uveitis, although therapy appears to become less effective in the long-term. The main drawbacks of this study were its small sample size, wide age-group range, and lack of long-term follow-up.

- In an open-label, comparative, multi-center, cohort study of childhood chronic uveitis, Simonini et al (2013) compared the effectiveness of adalimumab when used as first anti-TNFα therapy versus adalimumab used after the failure of a previous anti-TNFα (infliximab). A total of 26 patients (14 females, 12 males; median age of 8.6 years) with refractory, non-infectious active uveitis were enrolled. Due to the refractory course of uveitis to previous DMARD treatment, group 1 received adalimumab (24 mg/sq mt, every 2 weeks), as first anti-TNFα choice; group 2 received adalimumab, as second anti-TNFα drug, due to the loss of efficacy of infliximab, administered after a period of at least 1 year. Both groups received adalimumab for at least 1 year of treatment. Primary outcome was, once remission was achieved, the time to a first relapse. A total of 14 children (10 with JIA, 3 with idiopathic uveitis, 1 with Behçet's disease) were recruited in group 1; 12 children (7 with JIA, 3 with idiopathic uveitis, 1 with early-onset sarcoidosis, 1 with Behçet's disease) in group 2. Group 2 showed a lower probability to steroid discontinuation during the first 12 months of treatment (Mantel-Cox $\chi^2$4.12, $p < 0.04$). In long-term follow-up, group 1 had higher probability of uveitis remission during the time of treatment on adalimumab (median ± SE: 18 ± 1.1 versus 4 ± 0.6 months, 95 % CI: 15.6 to 27.5 versus 2.7 to 5.2, Mantel-Cox $\chi^2$10.12, $p < 0.002$). The authors concluded that even if limited to a relatively small group, the findings of this study suggested a better efficacy of adalimumab when used as first anti-TNFα treatment in childhood chronic uveitis. They stated that “further studies in a large cohort, in a prospective fashion, preferably by a randomized clinical trial, focused on one disease entity with a sufficient sample size, seem to be advocated to address this point”.

- A consensus panel organized by the American Uveitis Society (Levy-Clarke, et al., 2014) provided recommendations for the use of TNF-α biologic agents in patients with ocular inflammatory disorders. The authors performed a systematic review of literature to generate guidelines for use of these agents in ocular inflammatory conditions. Recommendations were generated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) group criteria. The panel found that numerous studies including controlled clinical trials have demonstrated that anti-TNF-α biologic agents (in particular infliximab and adalimumab) are effective in the treatment of severe ocular inflammatory disease. Based on these studies, the panel made the following recommendations. Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease. Infliximab and adalimumab can be considered as second-line immunomodulatory agents for the treatment of uveitis associated with juvenile arthritis. Infliximab and adalimumab can be considered as potential second-line immunomodulatory agents for the treatment of...
severe ocular inflammatory conditions including posterior uveitis, panuveitis, severe uveitis associated with seronegative spondyloarthropathy, and scleritis in patients requiring immunomodulation in patients who have failed or who are not candidates for antimetabolite or calcineurin inhibitor immunomodulation. Infliximab and adalimumab can be considered in these patients in preference to etanercept, which seems to be associated with lower rates of treatment success.

- In a randomized, double-blind, placebo-controlled, parallel group, multi-center study, Chevalier et al (2014) examined the effectiveness of adalimumab in patients with painful refractory (non-responders to analgesics and NSAIDs) hand OA. Patients were randomized to: 1/1 adalimumab 40 mg for 2 subcutaneous injections at a 15-day interval or placebo and monitored for 6 months. The primary outcome was the percentage of patients with an improvement of more than 50 % in global pain (visual analog scale) between week 0 (W0) and week 6 (W6). Secondary outcomes included the number of painful joints, swollen joints, morning stiffness duration, patient and practitioner global assessments, functional indexes for hand OA, and consumption of analgesics. Analysis on the mean primary outcome measure was done on patients who received at least 1 injection. A total of 99 patients were recruited and 85 patients were randomized. Among them, 37 patients in the placebo group and 41 in the adalimumab group received at least 1 injection and were evaluated at W6 (n = 78) on the main effectiveness outcome. Mean age was 62 years, 85 % were women, and mean level of pain was 62 mm at W0. At W6, 35.1 % in the adalimumab group versus 27.3 % in the placebo group had a pain reduction greater than or equal to 50 % (RR 1.12 (95 % CI: 0.82 to 1.54; p = 0.48). There were no statistical differences for all secondary end-points. The rate of adverse events was similar in the 2 groups. The authors concluded that adalimumab was not superior to placebo to alleviate pain in patients with hand OA not responding to analgesics and NSAIDs.

- Suarez-Perez et al (2012) described the epidemiological and clinical characteristics of patients with pyoderma gangrenosum (PG) along with their experience of treating the condition in a referral hospital in Malaga, Spain. A retrospective, observational study was undertaken between January 2000 and December 2009 and included all patients diagnosed with PG. The incidence of PG in the authors’ reference population is 3.26 cases per million inhabitants per year. The most frequent concomitant systemic disease was UC (5 cases, 33 %). In 4 patients with that disease, PG appeared during a flare-up. In 80 % of cases, patients were not referred to a dermatologist during the initial phase of PG, and most referrals were from gastroenterology or general surgery (4 patients each, 52 %). The authors concluded that patients with PG were often referred to dermatologists by other specialists after a varying period of time has elapsed without achieving an accurate diagnosis. In these patients, especially those between 20 and 40 years of age, it is essential to rule out concomitant disease. Adalimumab is a good treatment option for PG.

- Gisondi and Girolomoni (2013) investigated the impact of TNF-alpha antagonists on health-related quality of life (HRQoL) in selected skin diseases, i.e., chronic plaque psoriasis, Behcet's disease (BD), hidradenitis suppurativa (HS) and PG (PG). These investigators carried out a systematic literature search of Medline (2000 to April 2013) using the Cochrane highly sensitive and specific search strategy. Citations were screened for randomized, controlled trials of TNF-alpha antagonists (adalimumab, etanercept and
infliximab) versus placebo in adults with psoriasis, BD, HS or PG. From the literature it is evident that skin diseases can affect physical, psychological, social and occupational aspects of everyday life. Tumor necrosis factor-alpha antagonists induced consistent benefits across health outcomes in psoriasis, but only monoclonal antibodies, infliximab and adalimumab were effective in improving QoL in patients with BD, HS and PG. Dermatology Life Quality Index was the most common used tool for investigating HRQoL. For the majority of patients with skin diseases, the most important negative impacts on QoL were appearance related. Generally, the burden on QoL was correlated to the severity of skin disease and the improvement in QoL achieved by TNF-alpha blockers was proportional to the degree of disease remission. In general, achieving the highest clearing of skin disease with anti-TNF-alpha agents is required for optimal improvement in QoL.

- Agarwal and Andrews (2013) provided an up-to-date review of the published treatment effectiveness of currently available therapies for IBD-related PG in the biologic era. Systematic review of cases published post-2003 since the broad availability of anti-TNF-alpha therapy. Cases that did not have co-existent IBD, were non-English language, of pediatric age or without data on response to therapy were excluded. A total of 60 cases were identified; 55 % female, 50 % UC, 45 % CD, 5 % IBD-U. At PG diagnosis, 58 % had active and only 15 % inactive IBD, with 27 % with IBD activity unspecified. Predominant sites were lower limb (48 %) and peristomally (25 %); 42 % had multiple lesions. In 12 %, trauma preceded PG. In 42 %, new PG appeared while on IBD-specific therapy, while 28 % were on no therapy and in 30 %, IBD therapy was unspecified. Of patients on no therapy at PG onset (n = 17), 16 healed; 7 with first- and 8 with second-line therapy. In total, 34/60 patients received infliximab, 4 received adalimumab, 2 had both; with 33 (92 %) responding to one or the other. There was no correlation of PG duration or size with healing times. The authors concluded that PG appears predominantly during active IBD and is seen equally in CD and UC. New PG may be a manifestation of recrudescent IBD or it follow trauma. Anti-TNF-alpha therapy as a first-line agent for PG should be considered, as it appears to be highly effective.

- Arguelles-Arias et al (2013) examined the characteristics of PG associated with CD or UC and which treatments were prescribed in Spanish clinical practice. In this retrospective, observational study, the medical records from all patients with IBD and a diagnosis of PG attended by the gastroenterology departments of 12 Spanish hospitals were reviewed. Data on patient demographics and characteristics, underlying IBD and treatment, and PG characteristics, treatment, and outcome were collected and analyzed. The data from 67 patients were analyzed (41 [61.2 %] women, 41 [61.2 %] with CD, 25 [37.3 %] with UC, and 1 [1.5 %] with indeterminate disease). The underlying disease was in remission in approximately 1/3 of patients at the time of presentation of PG. Healing was achieved in all patients (in 3 without any systemic therapy). Oral corticosteroids were taken by 51 patients (76.1 %), almost always as first-line treatment, although definitive healing was attained in 19 (28.4 %). Biologic agents such as infliximab and adalimumab were taken by 31 patients (46.3 %) at some point (first-line in 6 patients [9.0 %]), with definitive healing in 29 patients (93.5 %). The authors concluded that oral
corticosteroid therapy remains the most common treatment for PG associated with IBD. Biologic therapies such as infliximab and adalimumab should also be considered.

- Marzano et al (2013) stated that PG and Sweet's syndrome (SS) are skin diseases usually presenting with recurrent ulcers and erythematous plaques, respectively. The accumulation of neutrophils in the skin, characteristic of these conditions, led to coin the term of neutrophilic dermatoses to define them. Recently, neutrophilic dermatoses have been included in the group of auto-inflammatory diseases, which classically comprises genetically determined forms due to mutations of genes regulating the innate immune response. Both PG and SS are frequently associated with IBDs; however, IBD patients develop PG in 1 to 3% of cases, whereas SS is rarer. Clinically, PG presents with deep erythematous-to-violaceous painful ulcers with well-defined borders; bullous, pustular, and vegetative variants can also occur. Sweet’s syndrome is characterized by the abrupt onset of fever, peripheral neutrophilia, tender erythematous skin lesions, and a diffuse neutrophilic dermal infiltrate. It is also known as acute febrile neutrophilic dermatosis.

Treatment of PG involves a combination of wound care, topical medications, antibiotics for secondary infections, and treatment of the underlying IBD. Topical therapies include corticosteroids and the calcineurin inhibitor tacrolimus. The most frequently used systemic medications are corticosteroids and cyclosporine, in monotherapy or in combination. Dapsone, azathioprine, cyclophosphamide, methotrexate, intravenous immunoglobulins, mycophenolate mofetil, and plasmapheresis are considered second-line agents. Hyperbaric oxygen, as supportive therapy, can be added. Anti-TNF-alpha agents such as etanercept, infliximab, and adalimumab are used in refractory cases. Sweet’s syndrome is usually responsive to oral corticosteroids, and the above-mentioned immunosuppressants should be considered in resistant or highly relapsing cases.

- Also, an UpToDate review on “Pyoderma gangrenosum: Treatment and prognosis” (Schadt, 2014) states that “Second line and adjunctive therapies -- In addition to infliximab, other biologic TNF-alpha inhibitors may be beneficial in PG. Adalimumab (40 mg weekly, 40 mg twice monthly, and other regimens) has been associated with ulcer healing in case reports. Most of the published cases have involved patients with concomitant inflammatory bowel disease or rheumatoid arthritis. Improvement in PG with etanercept (25 to 50 mg twice weekly) has also been reported in a small retrospective series and case report. However, in our experience, adalimumab seems to be more efficacious”.

- Sotiriou et al (2012) evaluated the safety and effectiveness of adalimumab using a higher dosage regimen for the treatment of hidradenitis suppurativa (HS) and established the recurrence-free interval after treatment discontinuation. Patients with moderate-to-severe HS were treated with 80 mg adalimumab at baseline, followed by 40 mg every week for 24 weeks. Subsequently, patients entered an observational period for another 24 weeks. Clinical evaluation took place every 4 weeks during the study period. Sartorius scoring system was used as assessment tool regarding disease activity. At the same time points patients evaluated disease activity by visual analog scale (VAS). They completed a Dermatology Life Quality Index (DLQI) questionnaire at baseline and at weeks 24 and 48. A total of 15 patients completed the study. Significant reduction in Sartorius score was obtained by week 24 with a marked improvement during the first month. Mean time
to relapse was 11 weeks after treatment cessation, but even at the final visit Sartorius score was significantly lower than at baseline. VAS score and DLQI showed a significant decrease at week 24. There was significant worsening at week 48, however both scores remained significantly lower than baseline levels. The authors concluded that these findings demonstrated the significant efficacy of the once weekly regimen, as well as its benefit regarding time to recurrence. However, they stated that the question if benefit outweighs the risk of a long-term anti-TNF-α antagonist's administration needs still to be answered.

- In a phase II, parallel, randomized, placebo-controlled trial consisting of a blinded 16-week period (period 1) and an open-label 36-week period (period 2), Kimball et al (2012) evaluated the safety and effectiveness of adalimumab in patients with moderate to severe HS. A total of 154 adult patients with moderate to severe HS who were unresponsive or intolerant to oral antibiotics were included in this study. Patients were assigned in a 1:1:1 ratio to adalimumab, 40 mg/wk; adalimumab, 40 mg every other week (EOW); or placebo. All patients received adalimumab, 40 mg EOW, at the beginning of period 2 but switched to weekly dosing if the response was suboptimal (HS Physician's Global Assessment [PGA] score of moderate or worse) at weeks 28 or 31. The primary outcome measure (clinical response) was the proportion of patients achieving an HS-PGA score of clear, minimal, or mild with at least a 2-grade improvement relative to baseline at week 16. At week 16, 3.9 % of placebo patients (2 of 51), 9.6 % of EOW patients (5 of 52), and 17.6 % of weekly patients (9 of 51) achieved clinical response (EOW versus placebo strata-adjusted difference, 5.6 % [95 % CI: -4.0 % to 15.3 %]; p = 0.25; weekly versus placebo strata-adjusted difference, 13.7 % [CI: 1.7 % to 25.7 %]; p = 0.025). Serious adverse event rates were 3.9 %, 5.8 %, and 7.8 % for placebo, EOW, and weekly patients, respectively (EOW versus placebo difference, 1.8 % [CI: -6.4 % to 10.1 %]; weekly versus placebo difference, 3.9 % [CI: -5.2 % to 13.0 %]). Significantly greater improvements in patient-reported outcomes and pain were seen in the weekly dosing group than in the placebo group. A decrease in response was seen after the switch from weekly to EOW dosing in period 2. The authors concluded that adalimumab dosed once per week alleviates moderate to severe HS. Drawbacks of this study were (i) weeks 16 to 52 of the study were open-label, (ii) the study was not powered to assess the risk for known serious adverse effects of adalimumab, such as tuberculosis, other serious infections, and demyelinating disorders.

- van Rappard et al (2013) provided an overview of the current evidence regarding off-label treatment of HS with TNF-α inhibitors; a systematic search was performed in MEDLINE, EMBASE and CENTRAL. Any type of original article concerning HS patients treated with infliximab, etanercept and/or adalimumab was included. No language restriction was applied. After full-text screening 65 studies involving 459 patients met the inclusion criteria and were subjected to data extraction. Four randomized controlled trials (RCTs) were available, and the remainders were case series or reports. Only RCTs were subjected to methodological quality assessment. Based on efficacy data extracted from the case reports, a moderate to good response was seen in 82 % of the patients treated with infliximab, 76 % of the patients treated with adalimumab, and 68 % of the patients treated with etanercept. Due to the moderate level of evidence only a weak
recommendation can be provided. If conventional treatment options fail, the use of TNF-α inhibitors can be a useful supplement for the treatment of recurrent severe HS. Infliximab should be preferred based on the most encouraging results regarding efficacy and expenses. Also adalimumab seems promising when administered in higher doses. The use of etanercept should be discouraged.

- Blok et al (2013) noted that HS is a difficult disease to treat. Although the pathogenesis of this inflammatory skin disease is largely unknown, the important role of the immune system has been demonstrated in both experimental and clinical studies. Clinicians are therefore increasingly prescribing systemic treatments with immunosuppressive agents, but the more traditionally used systemic retinoids, especially isotretinoin, also remain relatively common therapies. In order to provide an overview of all currently available systemic immunosuppressive agents and retinoids for the treatment of HS, a systematic search was performed using the Medline and Embase databases. All published papers concerning systemic retinoids or immunosuppressive treatments for HS in adults were included. The primary endpoints were the percentages of significant responders, moderate responders and non-responders. Other endpoints were the relapse rate and adverse events. In total, 87 papers were included, comprising 518 patients with HS who were treated with systemic retinoids, biological agents or another immunosuppressive agents, including colchicine, cyclosporine, dapsone or methotrexate. The highest response rates were observed with infliximab, adalimumab and acitretin. Overall, the quality of evidence was low and differed between the agents, making direct comparisons difficult. However, based on the amount of evidence, infliximab and adalimumab were the most effective agents. Acitretin was also effective in HS, although the quality of the evidence was low. The therapeutic effect of isotretinoin is questionable. Randomized controlled trials are needed to confirm the effectiveness of acitretin, and to identify the most effective immunosuppressive agents in HS.

- Samycia and Brassard (2013) high-lighted the use of biologic agents for the treatment of recalcitrant HS. These investigators reported on a 48-year old male with a 15-year history of refractory perianal-inguinal-buttock HS who, despite receiving numerous surgical drainages and traditional medical treatment for HS, still had severe pain. After trialing etanercept and infliximab with methotrexate, the patient had marked improvement with adalimumab. A literature review of biologics therapy was also performed. After trialing many traditional therapies, these researchers found that adalimumab appears to be the most effective treatment modality for the patient. A literature search revealed 53 articles on biologics therapy in HS. These articles were summarized. The authors concluded that biologic agents have been shown to have variable results in the treatment of refractory HS. Enough low-grade evidence has been accumulated to make the use of these agents suitable in HS. Moreover, they stated that until more clinical trials are performed on this topic, physicians should use clinical judgment when treating HS with biologic agents and be cautious by watching for significant adverse effects.

- Martin-Ezquerra and associates (2014) performed a retrospective study from 7 tertiary Spanish centers reviewing the charts of patients with HS treated with biological drugs. Retrieved information included epidemiological data, clinical features, pain intensity, Hurley stage, laboratory data and therapeutic outcomes. A total of 19 patients were
included in the study; 10 men (52.6%) and 9 women. Eight patients (42%) showed a Hurley severity stage II and 11 a stage III (57.8%). Adalimumab was prescribed as the first biological treatment in 9 out of 19 cases (47.3%), whereas infliximab was prescribed in 7 cases (36.8%), ustekinumab in 2 cases (10.5%) and etanercept in 1 (5.2%). A complete response was observed in 3 patients (2 cases with infliximab and 1 case with ustekinumab), a partial improvement in 10 patients and in 6 patients no clinical improvement was noted. One patient referred worsening of the skin symptoms. In 6 cases, a 2nd biological treatment was prescribed. In 3 of such cases, a partial improvement was noted, whereas in 3 cases no clinical improvement was observed. In 2 cases a switch to a 3rd biological drug was indicated, with a partial improvement in 1 case. The authors concluded that biological drugs could be a potential and effective therapeutic option for patients with severe HS. Complete and persistent clinical responses were rarely obtained (15%) and partial responses were achieved in approximately 50% of patients. No specific markers for a therapeutic response have been identified. No definitive conclusions regarding the most effective biological drug for HS could be drawn. Higher dosage schedules seem to be associated with higher response rates. The lack of response of one particular drug does not preclude a potential efficacy to another biological treatment.

• Moreover, an UpToDate review on “Treatment of hidradenitis suppurativa. (acne inversa)” (Margesson and Danby, 2014) states that “The main pharmacologic agents utilized for the management of severe and refractory disease are biologic therapies and oral retinoids. Based upon the data in support of its efficacy, infliximab is considered a first-line pharmacologic agent for the treatment of severe and refractory HS/AI. However, the requirement for intravenous administration, the presence of patient-specific contraindications, and the expense of the drug prohibits treatment in some patients. Alternatives to infliximab include adalimumab and acitretin. However, the data in support of these agents are less robust than for infliximab therapy. Ustekinumab, a newer biologic agent, has demonstrated benefit in small numbers of patients”.

• An UpToDate review on “Approach to the patient with a scalp eruption” (Goldstein and Goldstein, 2014) noted that dissecting cellulitis of the scalp presents as deep-seated nodules, pustules, and cysts in adults. These can heal with scarring, sinus tract formation, and significant, often permanent, alopecia. The culture is frequently negative or grows normal skin flora. There is vigorous granulomatous inflammation in this condition, which is typically managed with chronic oral antibiotics or isotretinoin. The review does not mention adalimumab as a therapeutic option.

• In a double-blind, multi-center RCT, Seror et al (2014) evaluated the effect of adding a 10-week treatment of adalimumab to a standardized treatment with corticosteroids on the ability to taper more rapidly corticosteroid doses in patients with newly diagnosed giant cell arteritis (GCA). Patients were randomly assigned to receive a 10-week subcutaneous treatment of adalimumab 40 mg every other week or placebo in addition to a standard prednisone regimen (starting dose 0.7 mg/kg per day). The primary end-point was the percentage of patients in remission on less than 0.1 mg/kg of prednisone at week 26. Analysis was performed by intention-to-treat (ITT). Among the 70 patients enrolled (adalimumab, n = 34; placebo, n = 36), 10 patients did not receive the scheduled
treatment, 7 in the adalimumab and 3 in the placebo group. By ITT, the number of patients achieving the primary end-point was 20 (58.9 %) and 18 (50.0 %) in the adalimumab and placebo arm, respectively (p = 0.46). The decrease in prednisone dose and the proportion of patients who were relapse-free did not differ between the 2 groups. Serious adverse events occurred in 5 (14.7 %) patients on adalimumab and 17 (47.2 %) on placebo, including serious infections in 3 patients on adalimumab and 5 on placebo. Two patients died in the placebo arm (septic shock and cancer) and 1 in the adalimumab group (pneumonia). The authors concluded that in patients with newly diagnosed GCA, adding a 10-week treatment of adalimumab to prednisone did not increase the number of patients in remission on less than 0.1 mg/kg of corticosteroids at 6 months.

- Chiu et al (2013) stated that drug concentration monitoring may be useful to guide therapeutic adjustments for anti-TNF agents in CD. The relationship between serum adalimumab concentrations and clinical outcomes was assessed using data from CLinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease (CLASSIC) I/II. Serum adalimumab concentrations at week 4 of CLASSIC I and weeks 4, 24, and 56 of CLASSIC II were compared by clinical remission status (yes/no). Logistic regression and Classification and Regression Tree analyses explored factors associated with remission at weeks 4, 24, and 56. Threshold analyses and receiver operating characteristic curves evaluated the relationship between serum concentrations and clinical remission/response. Serum adalimumab concentrations for 275 patients were available. Median adalimumab concentrations were significantly higher in patients who achieved clinical remission than those who did not at week 4 of CLASSIC I (8.10 versus 5.05 µg/ml, p < 0.05). At all time-points, adalimumab concentrations demonstrated considerable variability and overlap between patients with and without remission. With Classification and Regression Tree analyses, baseline Crohn's Disease Activity Index, baseline CRP, and adalimumab concentrations were associated with early remission at week 4 of CLASSIC I and week 4 of CLASSIC II, but not at weeks 24 and 56. Receiver operating characteristic curves demonstrated low utility of cut-off thresholds to discriminate by clinical response/remission status. The authors concluded that a positive association between serum adalimumab concentration and remission was identified at several time-points. A threshold concentration reliably associated with remission was not identified. They stated that further prospective evaluations are needed before recommendations for adalimumab concentration monitoring can be made.

- Mahil et al (2013) examined the association between serum adalimumab and etanercept levels, antidrug antibody levels and clinical response in a cohort of patients with psoriasis using a commercially available enzyme-linked immunoassay. In a single-center cohort of 56 adults with chronic plaque psoriasis initiated on adalimumab or etanercept monotherapy between 2009 and 2011, drug and antidrug antibody levels were measured at the patients' routine clinic reviews (4, 12 and 24 weeks of treatment and the last available observation). Patients' responses at 6 months were stratified into responders [75 % reduction in Psoriasis Area and Severity Index from baseline (PASI 75) or Physician's Global Assessment score of “clear” or “nearly clear”] and non-responders (failure to achieve PASI 50). After 4 weeks, adalimumab levels were significantly higher in responders compared with non-responders (p = 0.003) and these higher levels were
sustained at 12 and 24 weeks. Anti adalimumab antibodies were detected in 25% of non-responders (2 of 8 patients, average 22.5 weeks' follow-up) and none of the responders (n = 23, average 26.1 weeks' follow-up). There was no significant association between etanercept levels and clinical response at 4 weeks (p = 0.317) and no anti-etanercept antibodies were detected. Lack of serum trough levels may have resulted in underestimation of the prevalence of antidrug antibodies. The authors concluded that early adalimumab drug level monitoring at 4 weeks may be useful in predicting treatment response and potentially reduce drug exposure (and associated cost) with earlier review of treatment in those with low levels. No conclusions about the value of etanercept drug monitoring can be made due to the paucity of data. Moreover, they stated that larger studies are needed to assess the clinical utility and cost-effectiveness of these assays in personalizing therapy in psoriasis.

- Furthermore, the Product Insert of Humira (adalimumab) does not mention Anser ADA, and monitoring of drug level.  

References


95. Schadt C. Pyoderma gangrenosum: Treatment and prognosis. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2014.
Appendix

Information about the Psoriasis Area and Severity Index (PASI) and the Physicians' Global Assessment (PGA) is available from the following reference (Feldman & Krueger, 2005): http://ard.bmj.com/cgi/content/full/64/suppl_2/ii65.

Reviewed by a Board Certified Internist
Reviewed by David Evans, MD, Medical Director, Active Health Management- Dec 2016
Copyright 2016 ACTIVEHEALTH MANAGEMENT
No part of this document may be reproduced without permission.

Footnotes

[A] Further treatment is not considered medically necessary for persons whose psoriasis has not adequately responded after 12 weeks [A in Context Link 1]
Codes

CPT® or HCPCS: 96372, J0135, S9359, J0135