

## **The evidence base and rationale for the use of anti-TNF $\alpha$ biologic drugs for the treatment of Hidradenitis Suppurativa: an advocacy report from the Hidradenitis Suppurativa Foundation, Inc. by Howes, RJ; Barlow, M. May 9, 2007.**

There is an evidence base and rationale for the off-label use of anti-TNF $\alpha$  biologic drugs in the treatment of Hidradenitis Suppurativa (HS). There is a lack of medications approved specifically for the treatment of this disease. Those with HS may require increased and improved health services & improvements to their insurance coverage. These improvements to a HS patients quality of life, and quality of medical care will require major funding increases of disease-specific basic research which leads to large-scale multi-center clinical trials in order to investigate the use of biologic drugs for HS.

Hidradenitis Suppurativa is a common, painful, debilitating, and chronic inflammatory skin disease affecting 1% of the global population, primarily occurring in inverse areas of the skin, e.g. axillae and groin. The disease is variable and recurrent. HS presents clinically with painful deep-seated follicular nodules, papules, pustules and abscesses, leading to suppuration, fibrosis, distortion, degradation and hypertrophic scarring of the skin. Patients may present with solitary or multiple lesions in one area, with lesions in many areas, or in more severe cases may have large, recurrent, draining lesions that incompletely heal. Treating HS is challenging and the efficacy of common medical treatments for this disease are unsatisfactory. Many patients may respond poorly or experience a relapse of the condition after treatment is discontinued.

Biologic medications have been used as an "off-label" treatment for Hidradenitis Suppurativa. An evidence-base and rationale for the use of anti-TNF $\alpha$  drugs in the management of HS is suggested by recent basic research, clinical trial enrollments, recently published views on the pathogenesis of HS and an association of HS with Crohn's Disease, and the efficacy of biologic treatments recorded in clinical and case studies. Approximately 55 patients are included in 2 current US clinical trials/clinical studies on the use of anti-TNF $\alpha$  drugs for HS, and 2 recently completed clinical trials of anti-TNF $\alpha$  treatment (one from the United States, and one from Greece). There are at least 24 recorded case studies of HS treated with anti-TNF $\alpha$  medications. There is also evidence that at least one US health insurance company provides insurance coverage of biologic drug therapy for HS. There is also evidence that decisions by health insurers, which deny coverage for the experimental and investigational treatment of HS with anti-TNF- $\alpha$  drugs may be appealed and overturned.

### **1. Expert opinions detailing the rationale for use of biologics in HS treatment. Basic research, recent publication of views on the pathogenesis of HS and an association of HS with Crohn's Disease may provide an evidence-base and rationale for the use of anti-TNF $\alpha$ drugs in the management of HS.**

1(a) Giamarellou-Bourboulis EJ, Antonopoulou A, Petropoulou C, Mouktaroudi M, Spyridaki E, Baziaka F, Pelekanou A, Giamarellou H, Stavrianeas NG. Altered innate and adaptive immune responses in patients with hidradenitis suppurativa. *Br J Dermatol.* 2007 Jan ; 156 (1):51-6.

Clinical study of blood samples in 53 patients with HS reveal the existence of alterations of the function of the innate immune system and to a lesser extent of the adaptive immune system in patients with hidradenitis suppurativa.

"The lack of a specific mechanism for the pathogenesis of hidradenitis suppurativa has led to the application of a variety of therapeutic approaches such as antibiotics and immunosuppressive therapies; all were proved of limited or no benefit. Anti-TNF- $\alpha$  strategies appear to be promising in the treatment of this disorder. Their effect might be compatible with the hypothesis of an autoimmune predilection in hidradenitis suppurativa. Furthermore, the disease may co-exist with Crohn disease, which is an autoimmune disorder, and pyoderma gangrenosum, in which derangements of the immune function have been reported.. these diminished immune responses may provide an adequate explanation for the high recurrence rates even in patients undergoing extensive surgical excision of the affected sites."

1(b) Fardet L, Dupuy A, Kerob D, et al. Infliximab for severe hidradenitis suppurativa: Transient clinical efficacy in 7 consecutive patients. *J Am Acad Dermatol.* 2007 Apr; 56(4):624-628.

"The primary lesion in HS is an occluding spongiform infundibulo-folliculitis leading to dilatation of the follicle followed by its rupture and leakage of contents (including keratin and bacteria) into the surrounding dermis. This induces a vigorous chemotactic response with an inflammatory cell infiltrate of neutrophils, lymphocytes, and histiocytes. Moreover, in the chronic phase of the disease, granuloma with giant cells may be seen. TNF- $\alpha$ , which induces proinflammatory cytokines and activates neutrophils and lymphocytes, also recruits inflammatory cells to sites of inflammation and, thus, contributes to granuloma formation. It may, therefore, play an important role in HS. Hence, TNF inhibition by infliximab may be beneficial."

1(c) Seksik P, Contou J, Cosnes A, Cosnes J. Hidradenitis Suppurativa and Crohn's Disease. In: Jemec G, Revuz J, Leyden J (eds). Hidradenitis Suppurativa. 1st ed. Heidelberg, Germany.: Springer, 2006 Sep:50-57.

This chapter discusses and affirms the association between these HS, and Crohn's Disease, an inflammatory bowel disease, an approved indication for anti-TNF $\alpha$  drugs.

1(d) Jacob S, Kerdel F. Biologics for Hidradenitis Suppurativa (Verneuil's Disease in the Era of Biologics). In: Jemec G, Revuz J, Leyden J (eds). Hidradenitis Suppurativa. 1st ed. Heidelberg, Germany.: Springer, 2006 Sep:145-149.

"The association of HS with Crohn's Disease suggests an inflammatory etiology. Anti-TNF $\alpha$  medications have been shown to induce durable remissions in patients with HS/CD. The efficacy of these biologics suggests a role for TNF $\alpha$  in the etiology and pathogenesis of HS. The efficacy of biologics in HS suggests a role for broadening the therapeutic applications of TNF $\alpha$  inhibitors."

**2. Evidence that there are ongoing clinical studies/trials investigating the use of anti-TNF $\alpha$  medications for HS. Approximately 55 patients are included in 2 current US clinical trials/clinical studies on the use of anti-TNF $\alpha$  drugs for HS, and 2 recently completed clinical trials of anti-TNF $\alpha$  treatment, one from the United States, and one from Greece.**

2(a) Current clinical trials/studies on the use of anti-TNF $\alpha$  biologics for HS

2(a)(i) Open Label Clinical Trial Etanercept for Treatment of Hidradenitis. PHASE II, April 2005 to April 2007. University of Pennsylvania, Dept. of Dermatology, Philadelphia, Pennsylvania, 19104, United States; Link <http://www.clinicaltrials.gov/ct/gui/show/NCT00107991>

Approximately 20 patients: clinical trial.

2(a)(ii) Research Study- Treatment of Hidradenitis Suppurativa with Etanercept injection. Combined patient randomization to either Etanercept or placebo followed by open-label Etanercept, Penn State College of Medicine, Department of Dermatology, Hershey, Pennsylvania, 17033, United States; Link: <http://www.hmc.psu.edu/dermatology/>

Preliminary report on clinical trial presented at- "Directions 2006: The first international hidradenitis suppurativa research symposium" Dessau,

Approximately 20 patients: clinical trial.

2(b) Recently completed clinical trials/studies on the use of anti-TNF $\alpha$  biologics for HS, results not yet published.

2(b)(i) Non Randomized, Open Label, Uncontrolled Study of the Safety and Efficacy of Etanercept for the Therapy of Hidradenitis Suppurativa Phase 2, Sep 2005 to May 2007. Department of Internal Medicine, University of Athens, Medical School, Athens, 124 64 Greece;

<http://www.clinicaltrials.gov/ct/gui/show/NCT00329823>

Approximately 10 patients: clinical trial.

2(b) (ii) Open-Label Assessment of the Efficacy & Safety of Efalizumab in the Treatment of Mod-Severe Hidradenitis Suppurativa PHASE 1, February 2005 to February 2006, New York University School of Medicine, Dept. of Dermatology, New York, New York, 10016, United States; Link <http://www.clinicaltrials.gov/ct/show/NCT00134134>  
Approximately 5 patients: clinical trial

**3. Case studies detailing the treatment of Hidradenitis Suppurativa with anti-TNF $\alpha$  medications and the investigation of the use of biologics. There exists twenty-one citations to at least 24 recorded case studies of Hidradenitis Suppurativa treated with anti-TNF $\alpha$  medications.**

2007

Moschella, S.L. Is there a role for infliximab in the current therapy of hidradenitis Suppurativa? A report of three cases. International Journal of Dermatology (In Press/Accepted for publication).  
Case studies: three patients

Usmani N, Clayton T, Everett S, Goodfield M. Variable response of hidradenitis suppurativa to infliximab in four patients. Clin Exp Dermatol. 2007 Mar; 32(2):204-205.  
Three Cases.

Yamauchi P. Adalimumab in the management of hidradenitis suppurativa Journal of the American Academy of Dermatology, 56:2 (Supplement 2):AB41 (February 2007)  
Single case study Infliximab and Humira treatment in one HS patient.

Fardet L, Dupuy A, Kerob D, et al. Infliximab for severe hidradenitis suppurativa: Transient clinical efficacy in 7 consecutive patients. J Am Acad Dermatol. 2007 Apr; 56(4):624-628. Also presented at "Directions 2006: The first international hidradenitis suppurativa research symposium" Dessau, Germany – march 30–April 2, 2006 Exp Dermatol. 2006 Jun; 15:478-482. <http://www.hs-foundation.org/>  
Review of seven consecutive patients treated with HS.

2006

Henderson R. Treatment of atypical hidradenitis suppurativa with the tumor necrosis factor receptor-fc fusion protein etanercept. J drugs dermatol. 2006; 5(10):1010-1011.  
Single case study.

Thielen, A.-M., Barde, C. & Saurat, J.-H. Long-term infliximab for severe hidradenitis suppurativa. British Journal of Dermatology Online Early 2006  
Single case study.

Moul,DK; Korman,NJ. Severe Hidradenitis Suppurativa Treated With Adalimumab Arch Dermatol 2006 142: 1110-1112  
Single case study.

Scheinfeld N Treatment of coincident seronegative arthritis and hidradentis supprativa with adalimumab JAAD 2006 07 (Vol. 55, Issue 1) p163-164  
Single case study.

Armario-Hita J, Fernandez-Vozmediano J. P525 Infliximab for the treatment of suppurative chronic hidradenitis. poster abstracts, American Academy of Dermatology, 64th annual meeting, March 3–7, 2006 San Francisco, CA. J Am Acad Dermatol. 2006 Mar; 54(3):AB57.  
Case studies: six patients

Robins D. P594 Successful treatment of hidradenitis suppurativa with efalizumab: A case report. poster abstracts, American Academy of Dermatology, 64th annual meeting, march 3–7, 2006 San Francisco, CA. J Am Acad Dermatol. 2006 Mar; 54(3):AB74

Single case study.

Cusack C, Buckley C. Etanercept: Effective in the management of hidradenitis suppurativa. Br J Dermatol. 2006 Apr; 154(4):726-9.

Retrospective study of Etanercept in six patients.

2005

Rosi YL, Lowe L, Kang S. Treatment of hidradenitis suppurativa with infliximab in a patient with crohn's disease. J Dermatol Treat. 2005; 16(1):58-62.

Single case study.

Ravat F, O'Reilly D, Handfield-Jones S. Recalcitrant hidradenitis suppurativa treated with adalimuab. J Am Acad Dermatol. 2005 March; 52(3 Supplement 1):P58.

Single case study one patient treated with infliximab and adalimumab.

Bouthors, J.; Heughebaert, C.; Courivaud, D.; Caron, C.; Modiano, P. Hidrosadenite suppuree traitee par infliximab Annales de Dermatologie et de Vénérologie - Octobre 2005 Vol 132 - N° HS3 - Octobre 2005 p. 248 - 248

Single case study.

Massarotti E, Sobell J. TNF-alpha blockers for hidradenitis suppurativa American College of Rheumatology 2004 meeting, October 16-21, 2004, San Antonio,

Case studies: two patients.

Suys,E.; d'Heygere,F. Infliximab voor acne inversa (alias Hidradenitis Suppurativa). Nederlands Tijdschrift Voor Dermatologie & Venereologie, Vol. 15, November 2005 p406-407

Single case study.

2004

Jurgensmeyer JC, Fleischer A. Clinical improvement of refractory hidradenitis suppurativa with etanercept • ABSTRACT. J Am Acad Dermatol. 2004 March; 50(3, Supp. 1):15.

Single case study.

Stipho,S.; Welch,R.;Feller,E.;Shah,SA. Hidradenitis Suppurativa in Crohn's disease responding to Infliximab Abstracts Submitted for the 69th Annual Scientific Meeting of the American College of Gastroenterology. American Journal of Gastroenterology 2004 October 99 (s10), S1-S335. doi: 10.1111/j.1572-0241.2004.001\_1.x

Single case study.

2003

Lebwohl B, Sapadin AN. Infliximab for the treatment of hidradenitis suppurativa. Journal- American Academy of Dermatology. 2003; 49(5):275-276.

Single case study.

Adams DR, Gordon KB, Devenyi AG, Ioffreda MD. Severe hidradenitis suppurativa treated with infliximab infusion. Arch Dermatol. 2003; 139(12):1540-1542.

Single case study.

Sullivan TP, Welsh E, Kerdel FA, Burdick AE, Kirsner RS. Infliximab for hidradenitis suppurativa. *Br J Dermatol.* 2003; 149(5):1046-1049.

Case studies: five patients.

Roussomoustakaki M, Dimoulios P, Chatzicostas C, et al. Hidradenitis suppurativa associated with crohn's disease and spondyloarthritis: Response to anti-TNF therapy. *J Gastroenterol.* 2003; 38(10):1000-1004.

Single case study.

2001

Martinez F, Nos P, Benloch S, Ponce J. Hidradenitis suppurativa and crohn's disease: Response to treatment with infliximab. *Inflamm Bowel Dis.* 2001; 7(4):323-326.

Single case study.

#### **4. Supporting evidence from one US health insurance company that there is consideration for insurance coverage of biologics for HS treatment.**

Paramount Health care-Ohio and Southwest Michigan Insurance coverage for Infliximab Sep 2005 "REMICADE Coverage of infliximab is recommended in those who meet one of the following criteria: Other Uses with Supportive Evidence-Hidradenitis suppurativa. Patient has tried one other therapy (eg, intralesional or oral corticosteroids, antibiotics, isotretinoin). Infliximab has been effective in treating hidradenitis suppurativa that was refractory to other therapies."

Source:

<http://www.paramounthealthcare.com/documents/Prescription%20Drug%20Program/Prior%20Auth%20Criteria%20Part%20D.pdf>

#### **5. Evidence that decisions by health insurers, which deny coverage for the experimental and investigational treatment of HS with anti-TNF-a drugs may be appealed and overturned.**

2006 Independent Medical Review Decision/Experimental Investigation: Overturns Health Plan Decision to deny Enbrel coverage for HS Department of Managed Care, State of California

Source: <http://wp.dmhc.ca.gov/imr/detail.asp?id=5691>

Physician 1: The patient is a 45-year-old male with longstanding nodulocystic acne and hidradenitis suppurativa. He has previously been prescribed numerous antibiotics without successful resolution of his symptoms. Accutane provided some benefit but had to be discontinued due to hypertriglyceridemia in spite of the concurrent administration of lipid lowering agents. Enbrel therapy has been recommended for the patient, but The Health Plan denied coverage due to the investigational nature of the therapy. The patient and his provider are without significant options other than tumor necrosis factor (TNF) inhibitors at this point in his treatment. The preliminary evidence does support the use of this therapy for the treatment of hidradenitis suppurativa, and it is a reasonable approach at this juncture. Therefore, I have determined that the requested therapy is likely to be more beneficial for treatment of the patient's medical condition than any available standard therapy. The Health Plan's denial should be overturned.

Physician 2: The patient is a 45-year-old male with extensive acne and hidradenitis suppurativa. He has taken numerous oral medications including corticosteroids, antibiotics and retinoids without benefit. The patient had some response to retinoids, but was unable to tolerate the side effect of hyperlipidemia. The patient's provider recommended treatment with Enbrel and submitted a request for authorization. The Health Plan denied the request citing the experimental/investigational nature of the therapy in this clinical setting. The patient has extensive follicular disease that is poorly controlled with standard treatment modalities. Hidradenitis is a rare condition and there are no randomized, placebo controlled trials of medications for its treatment. Journal publications are generally limited to case reports for uncommon conditions such as this one. Enbrel, although not FDA approved for the treatment of hidradenitis suppurativa, has been shown to be effective in several case reports. Because of the rarity of the diagnosis, there are no medications approved specifically for the treatment of hidradenitis suppurativa. Any treatment, including the medication that have been tried and failed, will likely be an offlabel application of the drug. A trial of Enbrel as proposed by the patient's provider is quite reasonable and medically appropriate. Based upon



the information set forth above, I have determined that the requested therapy is likely to be more beneficial for treatment of the patient's medical condition than any available standard therapy. The Health Plan's denial should be overturned.

Physician 3: The patient is a 45-year-old-male who suffers from cystic acne and hidradenitis suppurativa of the face neck, trunk and axillae. Treatment with Accutane resulted in improvement of his skin condition, however it produced severe hyperlipidemia. Prior treatment with various oral antibiotics was not effective. The patient has recently been treated with Rocephin, prednisone and dicloxicillin without benefit. His dermatologist has proposed a trial of Enbrel therapy. The Health Plan denied authorization for the treatment based on a determination that the proposed therapy is experimental/investigational. At this stage in the patient's treatment, all of the conventional modalities for the treatment of his hidradenitis suppurativa have been exhausted with disappointing results. There is simply no reasonable option other than TNF inhibitors such as Enbrel, that may afford the patient some relief from his symptoms. The medically monitored use of Enbrel has support in the literature and is a well reasoned approach. Accordingly, I conclude that the requested therapy is likely to be more beneficial for treatment of the patient's medical condition than any available standard therapy. The Health Plan's denial should be overturned.