NHS England

Evidence Review:

Infliximab for the treatment of hidradenitis suppurativa

NHS England

Evidence Review:
Infliximab for the treatment of hidradenitis suppurativa

First published:	November 2015
Updated:	Not applicable
Prepared by	Turnkey Clinical Evidence Review Team on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

Hidradenitis suppurativa (HS) is a chronic skin disease that causes abscesses and scarring on the skin- usually around the groin, buttocks, breasts and armpits. The disease tends to start in one area with the formation of a single, firm lesion. If the condition is not diagnosed or adequately controlled with medication, lesions are likely to become increasingly more common, spread to other areas of the body and grow in size. As the disease progresses, patients may also develop fistulas or sinus tracts, narrow channels that form under the skin and break out on the surface. Lesions, fistulas and sinus tracts are all prone to secondary infection which will usually require antibiotic treatment.

The condition in its severest form can have a very significant impact on quality of life, requiring hospital admissions and resulting in major impairment of physical and social functioning.

The exact cause of HS is unclear, however the lesions appear to be the result of blocked sweat glands and hair follicles. There are indications that genetic factors play a role in up to a third of patients, meaning the condition is more likely in those with relatives who are affected. The British Association of Dermatologists has also suggested that HS may be linked to Crohn's disease and have noted that many HS patients also suffer from another underlying autoimmune disorder.

Onset of HS is most common in late teens and early 20’s. HS outbreaks may persist for years with interspersed periods of inflammation. Early diagnosis is important as a successful combination of treatments can often help manage the condition and prevent the need for multiple surgeries. Due to the rarity and often embarrassing nature of the disease, many patients either don't seek diagnosis or are misdiagnosed.

Infliximab is a biologic therapy known to reduce the body's inflammatory response. There is substantive clinical evidence and experience of its effectiveness in other autoimmune disorders such as Crohn's disease and rheumatoid arthritis. For this reason, there is clinical interest in whether it may be an effective treatment option in patients with HS. Infliximab is not currently licenced for this indication and it is unlikely that an extension will be sought as the patent for infliximab has now expired and biosimilar products are now available.

2. Summary of results

The evidence review looked to answer the following key questions:

Research question 1: Is infliximab clinically effective in limiting the frequency and severity of flares and avoiding sequential surgery to affected areas in patients who have moderate (Hurley stage II) or severe (Hurley stage III) hidradenitis suppurativa (HS), despite optimised treatment with multiple conventional therapies?

Research question 2: Is infliximab a safe and well tolerated drug to use in patients with hidradenitis suppurativa (Hurley stage II-III)?

Research question 3: Are there any particular subgroups of patients with hidradenitis suppurativa (indicated by severity, co-morbidities and demographic factors) who are likely to benefit more from the use of infliximab?

Research question 4: Is infliximab cost effective in the treatment of hidradenitis suppurativa (Hurley stage II-III)?

In summary:

- There are predominantly level 2/3 studies to support the clinical effectiveness of infliximab in patients with moderate to severe hidradenitis suppurativa (HS), with one small (N=38) RCT. The RCT found non-significant difference at the initial primary endpoint however significant benefit was found in post hoc analysis.

- Infliximab appears not to be associated with significant adverse effects in the majority of patients, noting that there is a lack of long term studies . Hypersensitivity reactions to infliximab are not uncommon.

- There is insufficient evidence to identify subgroups of patients with moderate to severe HS who may benefit more from infliximab.

- To date, no studies have been identified which evaluate the cost effectiveness of infliximab in the treatment of HS.

Research question 1: Is infliximab clinically effective in limiting the frequency and severity of flares and avoiding sequential surgery to affected areas in patients who have moderate (Hurley stage II) or severe (Hurley stage III) hidradenitis suppurativa, despite optimised treatment with multiple conventional therapies?

The evidence on clinical effectiveness of infliximab in the treatment of patients with HS is limited to a small, single-centre RCT and (predominantly) level 3 studies. This is not unexpected given the rarity of this condition.

The majority of patients who received infliximab were not in remission and had failed to respond to conventional treatments (systematic antibiotics, steroids and/or retinoid). Grant et al. (2010) in a double blinded, randomised control trial (level 1-) (n=38) found non-significant benefit in patients receiving infliximab at initial primary end point analysis when compared to placebo. Post-hoc analysis however showed a significant benefit, with reduction in the HS severity index score of 25-50% $p<0.001$. These findings are consistent with several systematic reviews (Brunasso et al., 2011 and Blok et al., 2013, level 2- and 3 respectively) that consist predominately of case series and case studies, and have shown a significant to moderate response in up to 90% of the patients. All of the systemic reviews evaluated have incorporated the only one RCT conducted to date (Grant et al., 2010), with duplication of evidence.

The baseline scores of both dermatology life quality index (DLQI) and visual analogue scale (VAS), that assess pain, in HS is high. Grant et al. (2010) observed a significant improvement in the DLQI ($P=0.003$), VAS ($P<0.001$) and physicians global assessment score ($P<0.001$) in the infliximab treatment group at 8 weeks. They also found a reduction in inflammatory markers, erythrocyte sedimentation rate and C-reactive protein in the infliximab group. These findings are consistent with other reported case series and case studies (level 3), with majority of follow-up to one year.

Van Rappard (2012), a small (N=20) retrospective cohort study, compared treatment outcomes of infliximab with another biological therapy and found that at one year, infliximab was more effective than adalimumab. There is insufficient evidence to compare other biological therapies with infliximab in treating severe to moderate HS.

The majority of studies have used 5mg/kg of intravenous infliximab, induction therapy (0, 2 and 6 weeks), and if continued then maintenance therapy at 8 weekly cycles. Moriarty et al., (2014) (level 3) described in three patients a weaning of response at 4 weeks during maintenance therapy, and were subsequently changed to 4 weekly cycles with an improvement in symptoms. It is widely recognised that infliximab can potentially lead to a loss of response long-term, attributed to immunogenicity and development of drug antibodies. Pradela et al. (2012) (level 3) assessed long-term efficacy of infliximab in HS in 10 patients and observed that relapse occurred in 50% of patients after a median period of 37 weeks with a median disease free period of 16 weeks.

Research question 2: Is infliximab a safe and well tolerated drug to use in patients with hidradenitis suppurativa (Hurley stage II-III)?

In the majority of patients, infliximab appears not to be associated with significant adverse effects. It has been associated with infusion reactions, and Grant et al. (2010) (level 1-) reported hypersensitivity reactions in up to 22% of patients (4 patients). Cases of opportunistic infections, hepatitis, lupus, peripheral neuropathy and pulmonary embolism have also been reported. Scheinfeld et al. (2014) reported a case (level 3) of a patient with severe HS developing metastatic squamous cell carcinoma (SCC) during induction therapy with infliximab. It remains controversial whether infliximab promotes the development of SCC in HS.

The paradoxical effects of infliximab have been reported. Gori et al. (2012) reported a patient developing acne and Nuno et al. (2012) (level 3) describe a patient developing flexural psoriasis. Acaquacalda et al. (2015) described 3 patients out of 11 developing an acute and painful polyarthritis without a systematic reaction during treatment with infliximab, resolution of arthritic symptoms following cessation of two patients and one following treatment with another biological therapy. There is a lack of long-term studies evaluating the tolerance of infliximab in HS patients

Research question 3: Are there any particular subgroups of patients with hidradenitis suppurativa (indicated by severity, co-morbidities and demographic factors) who are likely to benefit more from the use of infliximab?

HS is associated with other inflammatory conditions, such as inflammatory bowel disease, SAPHO syndrome, psoriasis and pyoderma gangrenosum. A systemic review (level 3) evaluated the efficacy of infliximab in patients with HS and other inflammatory disease (Machet et al., 2013) and reported infliximab to be efficacious in 72% of the cohort (16/22 patients), with statistically insignificant higher failure rates when compared to patients with HS alone (27% vs 13%, P=0.1).

There is insufficient evidence to identify subgroups of patients with HS who may benefit more from infliximab. However, infliximab has been administered to patients with moderate to severe HS in all studies.

Research question 4: Is infliximab cost effective in the treatment of hidradenitis suppurativa (Hurley stage II-III)?

To date no studies have been identified which evaluate the cost effectiveness of infliximab in the treatment of HS.

3. Research questions

1. Is infliximab clinically effective in limiting the frequency and severity of flares and avoiding sequential surgery to affected areas in patients who have moderate (Hurley stage II) or severe (Hurley stage III) hidradenitis suppurativa, despite optimised treatment with multiple conventional therapies?
2. Is infliximab a safe and well tolerated drug to use in patients with hidradenitis suppurativa (Hurley stage II-III)?
3. Are there any particular subgroups of patients with HS (indicated by severity, co-morbidities and demographic factors) who are likely to benefit more from the use of infliximab?
4. Is infliximab cost effective in the treatment of hidradenitis suppurativa (Hurley stage II-III)?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the appendix.

Appendix

Level	Study design and intervention				Outcomes				Reference		Other	
Level of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
1-	systematic	Infliximab study 38 patients. RCT, Grant 2010	Infliximab 5mg/kg at weeks zero, two and six	Clinical effectiveness of the intervention	Dermatology Life Quality Index (DLQI) score	33 patients provided efficacy data. Improvement of DLQI by 8.4 DLQI points after 8 weeks, P=0.003	-	-	Ingram, John R.; Woo, Pick-Ngor; Chua, Ser Ling; Ormerod, Anthony D.; Desai, Nemesha; Kai, Anneke C.; Hood, Kerry; Burton, Tara; Kerdel, Francisco; Garner, Sarah E.; Piguet, Vincent. Interventions for hidradenitis suppurativa. Cochrane Database Syst Rev. 2015,	In the infliximab group by 8 weeks one patient developed hypertension requiring hospitalisation, and one patient became pregnant . In the open phase of trial 4 patients that had previously received placebo experienced infusion reaction with infliximab and withdrew. No tuberculosis reactivation or opportunistic infections during the 12 month trial period.	See results	Population: 38 adults with moderate/severe HS Comments: Authors highlighted the need for more clinical trial to aid treatment choices in HS. Describes small RCT, downgraded to 1-.
3	systematic	122 patients (22 cases with HS)	Infliximab 5mg/kg/day in majority of cases 0, 2 and 6	Clinical effectiveness of the intervention	To determine efficacy of infliximab in patients with HS and inflammatory disease	16/22 patients with inflammatory disease infliximab reported to be efficacious. The number of treatment failures were higher in the inflammatory disease and HS group than HS and non-disease group, although not significant, 6/22 (27%) vs 13/100 (13%) P=0.1	-	-	Machet, Laurent; Samimi, Mahtab; Delage, Maïa; Paintaud, Gilles; Maruani, Annabel. Systematic review of the efficacy and adverse events associated with infliximab treatment of hidradenitis suppurativa in patients with coexistent inflammatory diseases. J. Am. Acad. Dermatol.. 2013,	Prevalence of adverse events in the HS and inflammatory disease group was observed to be lower although not statistically significant than the prevalence of adverse events in patients with HS and no associated inflammatory disease, 3/22 vs 29/102 respectively P=0.14	See results	Population: 122 adults patients with HS who were resistant to conventional therapy. Inflammatory disease associated with HS in 22 cases, of which there were 11 cases of Crohn's disease, 5 cases of pyoderma gangrenosum, 3 cases of ankylosing spondylitis, 3 cases of ulcerative colitis, SAPHO syndrome and one case of psoriasis. Treatment prior to infliximab was mainly azathioprine, methotrexate, corticosteroids or antibiotics. Comments: The authors comment that the efficacy of infliximab was first suggested in patients with HS and Crohn's Disease. Review lacked significant details re: type of studies included and the definition of efficacy. No details of adverse events. Although this is a systematic review, it lacks detail and is predominately case reports, down graded to level 3.

1-	systematic	Included one study on infliximab and HS-Grant 2010 RCT	Infliximab (review included all TNFα antagonist includes etanercept and adalimumab)	Clinical effectiveness of the intervention	Dermatology Life Quality Index (DLQI) score	Infliximab tolerated and clinical improvement with significant reduction in DQLI and ESR.	-	-	Gisondi, P.; Girolomoni, G.. Impact of TNF-α antagonists on the quality of life in selected skin diseases. G Ital Dermatol Venereol. 2013	-	See results	Population: Adult patients with Behcet's disease, hidradenitis suppurativa and pyoderma gangrenosum Comments: Authors highlight that health related quality of life is important for assessment of overall burden of disease in dermatology. QoL is used to monitor therapeutic outcome in clinical trials. And the DLQI score >10 (max score 30, where a higher score means more impaired) is recognised by NICE/British society of Dermatology/European guideline as an independent eligibility criteria for use of systemic therapies and biologics in psoriasis. Included one study, RCT (as described).
1-	systematic	47 studies (n=147) 1 RCT (level A), 7 studies level B and 34 level C studies	Almost all patients received intravenous infliximab 5mg/kg at weeks 0, 2 and 6. In 10 studies treatment was discontinued after three administration. In 5 papers dosing schedules not clear in five studies. In 4 papers patients received methotrexate and in 2 papers Azathioprine, possibly to prevent formation of autoantibodies. One study concomitant treatment with prednisolone in one study, prednisolone and ciclosporin in one and azathioprine and methylprednisolone.	Clinical effectiveness of the intervention	Efficacy of treatment, classified as 'significant response' (defined as a reduction of Sartorius score ≥ 50%, improvement in quality of life >50% or stated by authors. Moderate response if score reductions <50% or defined as non-responders.	Of the 42 studies, n=147, 74 patients (50%) were significant responders, 57 patients (39%) moderate responders and 16 patients (11%) non responders.	Recurrence and relapse	10/131 (8%) had recurrence of HS during treatment and 26 (20%) of responders relapsed within 2 weeks to 3 years after discontinuation of treatment.	Blok, J. L.; van Hattem, S.; Jonkman, M. F.; Horváth, B.. Systemic therapy with immunosuppressive agents and retinoids in hidradenitis suppurativa: a systematic review. Br. J. Dermatol.. 2013	14 studies did not report adverse events, observed in 19 studies. 31 patients discontinued treatment due to adverse events. 14 non-specified side effects, 8 acute arthritis/myalgia, 7 with headaches, 5 hypersensitivity reactions, 4 influenza like illness, 3 numbness in legs/neuropathy, 3 skin rash, 3 dizziness, 3 asthenia, 1 anaphylactic shock, 1 pneumococcal sepsis, 1 tuberculosis infection, 1 pustular lesions on lower limbs, 1 fever, 1 hypertension, 1 colon cancer, 1 herpes zoster and 1 patient dyspnoea and one patient developed lupus like reaction	See results	Population: Adults (18+ years) with HS. Comments: Overall one level 1 and remaining low level studies. The majority of papers were case reports/series which carried publication bias. The study concluded that in HS, 89% patients responded to intravenous infliximab. Study recognised the need for randomised controlled clinical trials to identify the most effective therapy for HS. Included all fully published papers which reported on clinical effects of any systemic immunosuppressive agents or systemic retinoid in HS. Studies were excluded if not dealing exclusively with HS and there were insufficient details on: treatment in regimen, dosing, treatment duration and concomitant immunosuppressive medication.

1-	systematic	Included one RCT Grant et al 2010	Infliximab 5mg/kg week 0, 2, and 6 weeks	Clinical effectiveness of the intervention	Efficacy of infliximab (HS score)	At 8 weeks in the treatment group >50% improvement although difference not significant 27% vs 5.2% p=0.092. Report post hoc analysis infliximab more effective than placebo 25-50% improvement in HS score (60% vs 5.6% p<0.001)	Assessed Physician Global Assessment (PGA), DLQI and pain visual analogue scales (VAS)	Statistically significant difference in PGA, DLQI and VAS scores	Alhusayen, Raed; Shear, Neil H.. Pharmacologic interventions for hidradenitis suppurativa: what does the evidence say?. Am J Clin Dermatol. 2012	-	See results	Population: Adult patients with moderate to severe HS. Comments: Authors conclude that there is fair evidence to support the use of intravenous infliximab in the treatment of advanced HS (Hurley's stage II and III). Advise in view of cost and adverse effect profile should be reserved for patients with severe disease affecting daily activity and who have failed antibacterial therapy (level I/Grade B). Only includes one RCT (Grant et al.,2010) with intention to treat analysis. To note primary end point was not significant in the only RCT, it was only significant in post hoc analysis.
2-	systematic	On infliximab (2001-2011) 16 case series and 26 case reports + one RCT (n=114 pts)	Majority of studies used a dose of 5mg/kg of infliximab (3 studies dose increased to 7.5 or 10mg/kg). 35 patients (31%) received induction regime (3 infusions), 70 patients (61%) received induction and then maintenance treatment (16 studies 8weekly cycles). 9 patients (8%) no information re: duration of treatment	Clinical effectiveness of the intervention	Efficacy of infliximab	In 82% of patients (94 patients) moderate or good response. In 28% of patients (32 patients) response sustained > 3 months after discontinuation of treatment. In 18% of patients efficacy was poor or absent. In 15 patients response decreased during continuous treatment. Withdrawal of infliximab treatment and re-introduction because of recurrence in 6 patients	-	-	van Rappard, Dominique C.; Limpens, Jacqueline; Mekkes, Jan R.. The off-label treatment of severe hidradenitis suppurativa with TNF-α inhibitors: a systematic review. J Dermatolog Treat. 2013	19 studies reported adverse event. 23 patients (20%) had to discontinue infliximab. One patient died from pneumococcal sepsis (opportunistic infection) after receiving infusions for 2 years.	See results	Population: Adult patients with HS. Comments: Predominately level 3 evidence except one RCT (Grant et al.,2010). Efficacy of treatment was not quantified (qualitative or quantitative measures). Review downgraded to 2-.

1-	RCT	38 patients, infliximab group n=15, placebo group n=23	Double blind treatment phase for 8 weeks with infliximab 5mg/kg at 0, 2 and 6 weeks (induction course). Patients taking placebo opportunity to cross over to infliximab in open label phase. Maintenance regimen IFX every 8 weeks, through to week 22. Patients observed subsequently until week 52	Clinical effectiveness of the intervention	i) HS Severity Index Score at the end of double blind phase at 8 weeks. Composite score of 0-19 is mild, 9-12 is moderate and severe >13 ii) Response rates defined as at least 50% decrease from baseline in the HSSI score analysed on an intent to treat basis	i) At 8 weeks in the treatment group >50% improvement although difference not significant 27% vs 5.2% p=0.092. ii) Post hoc HSSI composite response analysis indicated signficant difference between the two groups. 60% of patients treated with infliximab responded with a 25% to <50% decrease in HSSI score compared with placebo 5.2%, p=<0.001). Withdrawal from trial: 5 (17%) placebo patients withdrew between weeks 0-8 because of worsening disease and not included in analysis. No withdrawal from infliximab group within the 8 week trial. In the infliximab treated group 73% of patients participated to week 22 and 20% (n=2) through the observational phase to week 52. 60% (n=9) withdrew consent between weeks 22 and 52. 7/9 of these patients continued with infliximab outside of trial. One patient at week 14 discontinued as a result of pregnancy. In the placebo group one patient withdrew after the crossover because of infusion reaction, remaining 74% of patients (n=17), 56% of patients (n=13) continued until week 30 and after this period 10 patients withdraw consent and continue with Infliximab outside of trial. Total of 17 patients withdrew from trial to continue with infliximab.	i) Dermatology life quality Index (DLQI) ii) Visual analogue scale (VAS) and iii) Physician Global assessment score iv) Inflammatory markers (erythrocyte sedimentation rate and C-reactive protein)	i) At 8 weeks the mean DLQI change in infliximab group was 10 (17.1 at baseline to 7.1 at wk 8) compared with 1.6 in placebo group (17.4 at baseline to 15.8 at week 8, P=0.003). Significant improvement in infliximab group when compared to placebo in the follow parameters, symptoms and feelings (P=0.004), daily activities (P=0.031), leisure (P=0.016), personal relationships (P=0.035) and work and school (P=0.037) ii) Patients self reported extent of pain in the VAS group significantly improved in the infliximab group (53.3 at baseline to 13.5, change of 39.8) when compared to placebo (baseline 49.7 to 49.2, mean change 0.6), P<0.001. iii) PGA scores were significantly lower in the infliximab group (1.8) compared with placebo treated patients (4.7), P<0.001. iv) Reduction of markers of inflammation in infliximab group. ESR in infliximab group decreased from 23 to 11.3, compared to an increase in placebo group 25.3 to 31.2., P=0.012. Similar changes observed in CRP in infliximab group 2.0 to 1.0 and placebo group from 3.6 to 4, P=0.062	Grant, Annika; Gonzalez, Tayler; Montgomery, Michael O.; Cardenas, Vanessa; Kerdel, Francisco A.. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. J. Am. Acad. Dermatol.. 2010	No unexpected adverse events reported during trial. In the initial infliximab group (n=15) patients report mild symptoms including influenza like illness, myalgia, dizziness and headache. Adverse events in placebo treated patients were higher and included nausea, influenza like illness, pyrexia, nasopharyngitis and dizziness. following crossover period AE included herpes simplex infection and influenza like illness. Infusion reactions were reported in 4 patients (22%). Serious events included hypertension and pregnancy in infliximab group and infusion reaction in placebo group requiring hospitalisation.	See results	Population: Patients with moderate to severe HS (in infliximab group 14/15 patients with severe HS), as defined by HS Severity Index (HSSI) score > 8 (HSSI score ranges from 0 to 19). Adults, mean age infliximab group 34 years and placebo group 33.2 years. In addition, patients had at least one of the following i) HS duration longer than 1 year with multiple emergency department or doctor visits related to HS ii) intralesional steroid injections >5/year iii) failed systemic retinoid treatment within 3 months of trial iv) failed at least one prior course of antibiotic therapy (and not administered 2 weeks prior to entry into study) or v) history of reconstructive surgery but not within 3 months of entry. Exclusion criteria included: history of chronic or opportunistic infections within 6 months after last IFX infusion, history of lymphoproliferative disease or active malignancies, malignancy within previous 5 years, exposure to monoclonal antibody treatment or human/murine recombinant products or use of systemic anti inflammatory medications except low dose systemic steroids and/or non-steroidal anti-inflammatory drugs. Comments: Prospective double blind intention to treat study. Authors recognise that RCT is a single centre study, with patients treated by a single physician. Also acknowledge patients did not return after last infusion and HS Severity Index requires validation. Also the majority of patients withdrew from the study after the last infusion, so unable to determine time to rebound/relapse. This is a small study with a pre-specified primary end point showing no significance in outcome only significant in post hoc analysis.

3	cohort	67 patients (18 centres)	Pateints received anti-TNFα treatment, first line treatment the majority received infliximab 5mg/kg (n=57, 86.4%), 7 received Adalimumab and 2 received (No Suggestions).	Clinical effectiveness of the intervention	i) To assess efficacy of anti TNFα treatment , response after first line anti TNFα treatment divided into: 1) complete response with resolution of all skin lesion or at least 90% improvement. 2)partial response (at least 50% improvement) and 3) no response. ii) To assess event free survival and measured as date from beginning of treatment to date of first relapse or lost to follow-up	i) 8 patients (11.9%) achieved complete response, 31 (46.2%) partial response and 25 (37.3%) no response. 12 patients (17.9%) received two anti-TNFα drug treatments and 5 patients (7.4%) 3 drugs.	-	-	Sbidian, E.; Hotz, C.; Seneschal, J.; Maruani, A.; Amelot, F.; Aubin, F.; Paul, C.; Beylot Barry, M.; Humbert, P.; Dupuy, A.; Caux, F.; Dupin, N.; Modiano, P.; Lepesant, P.; Ingen-Housz-Oro, S.; Mahé, E.; Bachelez, H.; Chosidow, O.; Wolkenstein, P.. Anti-TNFα therapy for hidradenitis suppurativa. Results from a national cohort study between 2000 and 2013. Br. J. Dermatol.. 2015	4 patients had to stop anti-TNF α treatment because of severe adverse effects, included, hepatitis, lupus, repeated urinary tract infection and pulmonary embolism	See results	Population: Patients with moderate to severe HS- 16 patients with type II Hurley and 46 with type III Hurley. 37 were women (55.2%). 33 patients (49%) had associated inflammatory disorder: 2 patients with inflammatory bowel disease, 11 with inflammatory arthritis, 12 with inflammatory bowel diseases or arthritis and 8 with neutrophilic skin disease. Adults, median age 38 years (10.9-71.8 years). Comments: National retrospective cohort study, involving 18 centres (25 centres contacted) the median follow-up between the three grousp (responsive, partial response and no response) was variable, 22.8, 13.2 and 4.6 months respectively. The paper does not clearly delinate response rate amongst different type of anti -TNFα treatments, although majority of first line treatment was with infliximab. Study does not meet criteria for cohort study and therefore downgraded to 3. Low level evidence study

2-	cohort	20 patients (10 patient in each group)	In 2005 patients received 3 infusions of intravenous infliximab at 5mg/kg at weeks 0, 2 and 6.	Clinical effectiveness of the intervention	Assessed in each group i) Sartorius score ii) Dermatology Quality of life index (max score 30) iii) ESR and CRP changes iv) patient and doctor global assessment v) duration of efficacy	19 patients completed the study. In both groups the severity of HS diminished. i) The average Sartorius score was reduced to 54% of baseline for infliximab group (164±50 to 89±49 at 1 year, p=0.002) compared to 66% in Adalimumab group (170±48 to 113±73 after 1 year, p=0.02). ii) In the infliximab group the mean score of DQLI was 18.4±7.9 before treatment and improved to 9.3±9.1 (p=0.007) after one year. In the adalimumab group DQLI mean score before treatment was 13.3±7.1 and after 1 year to 11.7±9.9 (p=0.66). iii) In both groups initial reduction in inflammatory laboratory parameters. After 1 year reduction of the infliximab group remained significant. In the infliximab the ESR group 31.8 before treatment to 14.5 at one year (p=0.05) and CRP reduced from 31.7 to 8.9 after one year (p=0.03). In the Adalimumab group mean ESR reduced from 36.2 to 33.9 at 1 year (p=0.8), and CRP reduced from 22.5 to 24.6 after 1 year (p=0.7). iv) Patients rated the efficacy of treatment on a 10-point scale. In the infliximab group what mean score after one year was 7.2±2, and in the Adalimumab group was 5.1±2.8. Doctor global assessment performed after 1 year using a 4 point scale. In the infliximab group the mean score was 3.2±0.6 and Adalimumab group the mean score was2.2±0.8.	-	-	van Rappard, Dominique C.; Leenarts, Marjolein F. E.; Meijerink-van 't Oost, Leonie; Mekkes, Jan R.. Comparing treatment outcome of infliximab and adalimumab in patients with severe hidradenitis suppurativa. J Dermatolog Treat. 2012	No serious adverse events. One patient in the infliximab developed an acute arthritis and myalgia. Three patients in the adalimumab group complained of fatigue directly after treatment.	See results	Population: Two cohorts of 10 adult patients suffering from severe, recalcitrant HS were compared. Ten patients treated with infliximab (6 females and 4 males) and 9 patients with adalimumab (1 female, 8 males). Adults treated with infliximab (average age 41 years) and adalimumab (average age 48 years). Comments: A retrospective cohort study, to note different time points for both infliximab (2005) and Adalimumab (2009). Authors concluded that Adalimumab 40mg SC every other week is less effective than infliximab IV 5mg/kg at weeks 0, 2 and 6. Small retrospective cohort study, patients were not treated and evaluated at the same time, study downgraded to 2-.
3	case series	10 patients	Patients received intravenous infliximab 5mg/kg at weeks 0, 2, 6 and then every 8 weeks.	Clinical effectiveness of the intervention	Assessment of efficacy was based on i) response: At least 50% decrease from baseline in the HSS after starting infliximab infusion. Ii) relapse defined as an increase of 40% of initial response achieved	Lack of response observed in 20% and relapse in 50% of patients. Two patients 20% discontinued treatment after five doses due to absence of response. Relapse occurred in 50% of patients after a median period of 37 weeks, median disease free period of 16 weeks. One patient recovered initial response after relapse. Median number of doses administered 7.5.	-	-	Paradela, Sabela; Rodríguez-Lojo, Romina; Fernández-Torres, Rosa; Arévalo, Pilar; Fonseca, Eduardo. Long-term efficacy of infliximab in hidradenitis suppurativa. J Dermatolog Treat. 2012	No infusion reactions or life threating adverse events detected. In two patients infliximab discontinued in two patients mycobacterial folliculitis and scrotal abscess swelling.	See results	Population: Adults aged 26- 60 years with moderate to severe refractory HS (Hurley stage II- III) , 6 females and 4 males. Where HS was present for at least 6 months and refractory to medical therapies and intralesional steroid injection. Also with multiple anatomic regions involved could not be easily cured by surgical treatment or history of failed treatment by CO2 laser or surgical drainage. Exclusion criteria included opportunistic infections, poorly controlled medical conditions, active tuberculosis, pregnancy or planned pregnancy, lactating women, history of lymphoproliferative disease or other malignancies, HIV, or virus B or C hepatitis infection. Comments: A long-term prospective study of 10 patients. There was a lack of a comparison between groups of patients. This is a low level evidence study.

3	case series	11 patients	Patients received intravenous infliximab 5mg/kg at weeks 0, 2, 6 and then every 8 weeks.	Safety of the intervention	Evaluating new articular inflammatory manifestations following treatment with infliximab. Side effects recorded and all patients with osteoarticular symptoms referred to department of Rheumatology	3/11 patients developed an acute and painful polyarthritis without a systematic reaction. Mean time between start of treatment and first arthritic symptoms (range 1-16) and after 4 infusions (range 1-8). Mean duration of arthritis symptoms was 3 months. Following cessation of treatment two patients improvement and one relieved with Adalimumab.	-	-	Acquacalda, Emilie; Roux, Christian Hubert; Albert, Christine; Breuil, Véronique; Passeron, Thierry; Euller-Ziegler, Liana. New onset of articular inflammatory manifestations in patients with hidradenitis suppurativa under treatment with infliximab. Joint Bone Spine. 2015	-	See results	Population: Adults with severe, therapy resistant HS (Hurley stage 3) and not responding to systemic antibiotics. Comments: Authors report that arthritis as a side effect of infliximab is not well known, although polyarthromyalgia has been described 12 days after 2nd dose of infliximab as a late hypersensitivity reaction. Authors comment on a potential paradoxical reaction with infliximab. This is a low level evidence study.
3	case series	19 patients (7 patients received infliximab as first line therapy)	7 patients received infliximab (36.8%). Adalimumab in 9 patients (47.3%), (No Suggestions) in 2 patients (10.5%) and one etanercept (5.2%)	Clinical effectiveness of the intervention	Clinical efficacy of biological treatment	i) 2/6 patients with infliximab had a complete response, 3/6 patients had a partial response and worsen in one patient ii) 6/9 patients in the adalimumab achieved a partial response and ineffective in 3/9 patients iii) Complete response in one patient and partial response in one after ustekinumab iv) One patient that received etanercept and found to be ineffective. In 6 patients a second biological treatment was administered with partial improvement in 3 and no clinical improvement in 3 patients. In 2 patients a switch to a third biological drug with a partial improvement in one patient	Pain assessment with Visual analogue scale of pain intensity (VAS) following treatment	On average the baseline VAS score was 7.3 points prior to treatment and following biological therapy reduced to 3.27points (SD 2.76). Average pain reduction was 6.5 in women and 1.4 in men (P=0.006)	Martin-Ezquerra, G.; Masferrer, E.; Masferrer-Niubò, M.; Ferran, M.; Sánchez-Regaña, M.; Collgros, H.; Bordas, X.; Notario, J.; Alsina, M.; Gil, I.; Izquierdo, N.; Aparicio, G.; Mollet, J.; Garcia-Patos, V.; Pujol, R. M.. Use of biological treatments in patients with hidradenitis suppurativa. J Eur Acad Dermatol Venereol. 2015	One patient developed severe infusion reaction during first dose of infliximab and withdrew.	See results	Population: Patients with severe HS. 10 men and 9 women. 8 patients (42%) and 11 patients with stage III (57.8%). Majority of patients had a concomitant illness: 3 patients with plaque type psoriasis, 2 with pilonidal cysts, 2 with rheumatoid arthritis, one with spondyloarthropathy, one with still disease and one with SAPHO syndrome. Patients prior to treatment with biological therapies were treated with different strategies including: wide spectrum antibiotics, oral retinoids, finasteride, zinc gluconate, cyclosporin A, colchicine, dapsone, oral and or intralesional corticosteroids. All patients required at least one surgical procedure. Comments: This is a small case series with significant bias and is therefore low level evidence.

3	case series	10 patients	10 patients received infliximab at weeks 0, 2 and 6 weeks, and then every 4 weeks. 8 patients treated for 1 year	Clinical effectiveness of the intervention	Evaluate clinical efficacy at 12 months	At one year the number of involved sites (P<0.001) and flares (P<0.05) decreased significantly. The mean baseline DLQI was 20 (range 9-30) which decreased to 6/30 following treatment with infliximab (P<0.001).	-	-	Lesage, Candice; Adnot-Desanlis, Lucie; Perceau, Géraldine; Bonnet, Morgane; Palot, Jean-Pierre; Bernard, Philippe; Reguiai, Ziad. Efficacy and tolerance of prolonged infliximab treatment of moderate-to-severe forms of hidradenitis suppurativa. Eur J Dermatol. 2012	4 minor infection, 1 pt developed hepatitis that rapidly resolved and one keratoacanthoma	See results	Population: Adults with moderate to severe forms of HS who were ineligible for surgery, or those who had relapsed after surgery. Comments: This is a small case series with significant bias and is therefore low level evidence.

3	case series	27 patients (compared to three control groups)	Infliximab treatment at 5mg/kg at weeks 0,2 and 6 and they every 2 months	Safety of the intervention	i) To determine the incidence of patients with HS developing arthritis after treatment with infliximab ii) compare group to control groups	27 patients treated with infliximab infusions (21.4 patients-years) i) 5/27 patients with HS (18%) developed an acute and painful polyarthritis during treatment with infliximab with it occurring on average after 12months and not directly related to anti-infliximab antibodies and resolved after 4 months. However in one patient that had been previously exposure to infliximab did have high titre anti-infliximab antibodies and diagnosis compatible with serum sickness. No patient had suffered from arthritis prior to treatment. ii) Arthritis was not observed in any of the control group. Odds ratio when compared with Adalimumab group and psoriasis groups was 7.24 [95% CI 1.15-45.6] and 9.02 [95% CI 1.45-55.82) respectively.	-	-	van Rappard, D. C.; Mooij, J. E.; Baeten, D. L. P.; Mekkes, J. R.. New-onset polyarthritis during successful treatment of hidradenitis suppurativa with infliximab. Br. J. Dermatol.. 2011	As per primary outcome	See results	Population: Patients with severe, therapy resistant HS (Hurley Stage III, not responding to combination of clindamycin and rifampicin). The control group of 227 patients with HS were not treated with any biological agents, group B included 22 patients treated with adalimumab and group C comprised 28 patients with psoriasis who were treated with infliximab Comments: Authors comment that arthritis is not a common known side effect of treatment with infliximab. Temporary arthralgia with fever and myalgia is a possible side effect with a frequency of 1:100 to 1:1000 that occurs 12 days after infusion and is regarded as a serum sickness type delayed allergic reaction. Authors acknowledge that the study is a small retrospective study and those in the treatment arm were closely monitored when compared to those patients with HS and not receiving biological therapy. Although none of the patients had developed arthritis prior to the infusions, HS is known to be associated with arthritis, although the aetiology remains unclear. Authors suggests a possible explanation of their findings may be a result of paradoxical reactions to TNF blockade. Study does not meet criteria for cohort study and is therefore a case series.

3	case series	6 patients	Biological agents, treated with Adalimumab, (No Suggestions) and infliximab	Clinical effectiveness of the intervention	Evaluate clinical efficacy	i) 4 patients treated with infliximab. 3patients had a good response, one patient had an early good response and then relapsed ii) 3 patients received Adalimumab, 2 patients observed a reduction in lesions and one patient treatment ceased after two months because of progressive disease and neurological adverse events iii) etanercept in one patient in reducing lesions and increased lesions noted 3 months after cessation of therapy	-	-	Chinniah, Niranthari; Cains, Geoffrey David. Moderate to severe hidradenitis suppurativa treated with biological therapies. Australas. J. Dermatol.. 2014	-	See results	Population: Patients with severe HS (Hurley stage III). 4/6 patients were men. Other comorbidities were co-existent commonly type II diabetes mellitus and acne conglobate. Median age 27.5 years (16-51 years) Comments: Only 4 patients received infliximab. Small case series. Low level evidence
3	case series	7 patients	Infliximab 5mg/kg infusions at week 0, 2, 6 and then 8 weekly, median of six infusions (range 3-19)	Clinical effectiveness of the intervention	To evaluate clinical efficacy. Reporting self improvement of HS in terms of pain, seeping and dermatology quality of life (DLQI)	6/7 patients reported improvement in DLQI, median DLQI score variation of 10 (range 0-15). The final median score was 8 (range 0-18). 6/7 of patients noted global improvement and no aggravation. Median change was 70% for global improvement and 70% for pain. None of the patients reported worsening of symptoms.	To evaluate changes in inflammatory markers, CRP levels and neutrophil counts	No significant changes in inflammatory blood marker values. Median CRP level was 6mg/l before treatment and 5mg/l after treatment. Median neutrophil count was 8.2x103/mm3 before treatment and 4.9x103/mm3 after treatment.	Delage, Maïa; Samimi, Mahtab; Atlan, Michaël; Machet, Laurent; Lorette, Gerárd; Maruani, Annabel. Efficacy of infliximab for hidradenitis suppurativa: assessment of clinical and biological inflammatory markers. Acta Derm. Venereol.. 2011	2/7 patients reported adverse events, one patient eczematous eruption and second patient cervical abscess	See results	Population: Moderate to severe HS (Hurley score II-III) resistant to several local and at least two 3 month long systemic treatments. 7 patients (4 women) and mean age 37 years. Comments: A retrospective study of patients consecutively receiving infliximab. This was a small case series and therefore is low level evidence

3	case report	1 patient	3 courses of infliximab 500mg	Safety of the intervention	Evaluating safety of drug	Undergoing surgical debridement of perineal and anal areas and at surgical debridement following 3rd dose, noted to have squamous cell carcinoma. infliximab ceased	-	-	Scheinfeld, Noah. A case of a patient with stage III familial hidradenitis suppurativa treated with 3 courses of infliximab and died of metastatic squamous cell carcinoma. Dermatol. Online J.. 2014	Patient developed SCC after 3rd dose of infliximab died after a year of ceasing medication. SCC had metastasised	See results	Population: One patient, aged 47 years, with familial HS (Hurley Stage III) involving groin, legs, buttocks and perineal areas. Patient had previously undergone numerous surgeries, course of antibiotics and had taken isotretinoin without long-term benefit. Comments: Authors report that although rare severe HS of the anal, perianal, gluteal, thigh and groin regions can evolve into squamous cell carcinoma (malignant degeneration), it does not usually occur until HS has been present for more than 20 years. Authors comment that it remains controversial to what extent infliximab promotes the development of SCC particularly in the setting of short term use. Possibly dampens the inflammatory response and that of DNA repair, the cause and effect relationship remains unclear. Case report reporting SCC. Low level evidence.
3	case report	1 patient	Infliximab initially at dose of 5mg/kg at weeks 0,2 and 6. Continued on maintenance infusion 8 weekly with an increased infliximab dose of 7.5mg/kg and then tapered. Restarted at dose of 5mg/kg every 8 weeks	Clinical effectiveness of the intervention	To evaluate clinical efficacy	Both diseases remitted, with complete restoration of skin integrity and resolution of chronic severe pain. Initial improvement following induction and subsequent resolution at one year. Dose was tapered and then subsequently discontinued. The patients disease relapsed approximately 7 months after discontinuation of infliximab and then recommenced resulting in resolution	-	-	Groleau, Patricia F.; Grossberg, Anna L.; Gaspari, Anthony A.. Hidradenitis suppurativa and concomitant pyoderma gangrenosum treated With infliximab. Cutis. 2015	No significant adverse events reported	See results	Population: One patient, aged 51 years, with pyoderma gangrenosum (PG) and hidradenitis Suppurativa (HS). Developed widespread inflammatory ulcers ~50% of body surface area with chronic severe pain. Initially treated with intravenous ampicillin-sulbactam and vancomycin and oral prednisolone 80mg daily for two weeks, with minimal improvement. Comments: Case report reported remission of two diseases. Low level evidence.

3	Case series	11 patients	All patients received infliximab at dose of 5mg/kg 0,2 and 6 and then 8 weekly. Changed from 8 weekly to 4 weekly and subsequently 8 patients received induction and 4 weekly cycles	Clinical effectiveness of the intervention	To evaluate clinical efficacy (4 weekly infliximab cycles)	Authors report 'weaning off' of infliximab effect with a disease flare approximately at 4 weeks that occurred at 9, 11 and 14 months after commencing infliximab in three patients that were initially on 8 weekly cycles. All patients an initial disease improvement as assessed by VAS, DLQI and physician assessment. Baseline average VAS for pain was 7.7 (6-10) and decreased to 3.4 (1-8), and DLQI median 28.6 (23-30) decreased to 12.9 (1-24). Two patients were observed to have secondary failure at 12 and 9 months.	-	-	Moriarty, B.; Jiyad, Z.; Creamer, D.. Four-weekly infliximab in the treatment of severe hidradenitis suppurativa. Br. J. Dermatol.. 2014	Patients required antibiotics for cutaneous infections (4 pts), respiratory tract infections (3 pts) and tonsillitis (1pt) and one patient developed Hodgkin Lymphoma 36 months after cessation of infliximab	See results	Population: Patients with severe HS (Hurley stage 3). 8/11 patients were male. 11 patients received prior treatments, 11 received systematic antibiotics and systematic retinoids. 7 patients received steroids. Majority of patients had co-morbidities, including: 8 patients with acne, 2 patients with cellulitis of the scalp, 1 patient with intestinal keratitis, 4 patients with inflammatory arthropathy, 4 patients with hypertension, 2 with type 2 diabetes, 1 patient with substance abuse, 1 with ischaemic heart disease. Average age 44 years (range 28- 69 years) Comments: Authors comment that although there may be association of other types of lymphoma with anti-TNFα antagonists, the risk of Hodgkin lymphoma was not perceived to be associated. Authors conclude that the optimal dosing schedule for use of infliximab in treatment of HS remains to be determined. Low level evidence study.
3	case report	1 patient	Infliximab 5mg/kg 8 weekly cycles	Safety of the intervention	To evaluate clinical efficacy	HS improved after the first infusion of Infliximab. 10 months after started treatment developed 'flexural' psoriasis that was treated with topical hydrocortisone 2.5%. Patient continued on infliximab.	-	-	Nuño-González, A.; Dehesa, L.; Ricotti, C.; Kerdel, F.. Flexural or inverse psoriasis in a patient with hidradenitis suppurativa receiving treatment with infliximab. Actas Dermosifiliogr. 2012	Paradoxical development of Psoriasis	See results	Population: Female obese non- smoking patient with HS diagnosed at age of 20, with progression of disease in the last 3 years. Prior treatment with broad spectrum antibiotics topical and oral. Comments: Case report, low level evidence

3	case report	1 patient	Infliximab infusions of 5mg/kg at weeks 0,2 6 and then 8 weeks	Clinical effectiveness of the intervention	To evaluate clinical efficacy, measured DLQI	Physician assessment at fourth infusion report clinical improvement, with healed inflammatory abscesses and granulomatous tissue. Baseline DLQI was 21 and after the third session improved to 0. Baseline inflammatory markers were ESR=80mm/h and CRP=80mg/l, with improvement following treatment ESR=25 and CRP=10	-	-	Gori, Alessia; Rossari, Susanna; Bruscino, Nicola; Tripo, Lara. Paradoxical effect of infliximab in a patient with hidradenitis suppurativa. Dermatol Ther. 2012	Patient developed acne following Infliximab	See results	Population: One male patient, aged 19 years old, with HS that occurred 5 years prior to puberty. Extensive fibrotic scars and deep abscesses with sinus tract and fistula formation. In addition inflammatory nodules and cysts, although with no central necrosis. Prior to infliximab treatment patient had been treated with combination of antibiotics and corticosteroids with no beneficial effects. Comments: Authors concluded that infliximab can be an effective therapy in HS patients but may develop paradoxical effect of facial acne lesions. Low level evidence study.
3	case report	1 patient	Infliximab infusions 5mg/kg at weeks 0,2 and 6, and 8 weeks thereafter.	Clinical effectiveness of the intervention	To evaluate clinical efficacy i) DQLI (quality of life index) ii)Visual analogue scale VAS (0=no pain, 10= very severe pain)	Patients DLQI score decreased from 24 at baseline to 4 after seven infusions and ii) VAS score decreased from 9.0 to 0.5. Patient reported no further need for pain medication after 2.5 months of treatments.	-	-	von Preussen, Anna Catharina Prinzessin; Flux, Katharina; Hartschuh, Wolfgang; Hartmann, Martin. Acne inversa successfully treated with infliximab. Int. J. Dermatol.. 2012	No adverse events report	See results	Population: Female patient, aged 47 years, with marked widespread skin lesions HS. Patient treated with oral rifampicin and clindamycin, and topical disinfectants. Comments: Single case report, low level evidence

3	Systematic	95 patients	44 patients (46.8%) followed an induction treatment (<4 infusions), 48 patients (51.1%)followed continuous treatment following induction (0.2.6 weeks) and in 2 patients schedule not available Mean number from 66 patients of infusions received was 4.9	Clinical effectiveness of the intervention	To evaluate clinical efficacy	i) In 61 patients, 52 patients (85.3%) reported a moderate or marked improvement during treatment, 8 patients (13.1%) little or no improvement. ii) Outcome evaluation at the end of follow-up was assessed in 66 patients, 7 patients (10.6%) had stable response after withdrawal, 4 (6.1%) stable whilst on therapy, 15 patients (22.7%) reoccurrence of lesion following cessation of treatment (mean time to reoccur was 28.2 weeks). In 8 patients (12.1%) response was lost during continuous treatment. 8 patients had no response and 31 patients no data regarding end of follow-up events	-	-	Brunasso, Alexandra M. G.; Massone, Cesare. Treatment of hidradenitis suppurativa with tumour necrosis factor-alpha inhibitors: An update on infliximab. Acta Derm. Venereol.. 2011	21 stopped therapy as a result of adverse events, 8 had infusion reactions, 2 had a diagnosis of cancer, 2 peripheral neuropathy, 1 patient with a lupus reaction, 1 generalised swelling, 1 anaphylactic reaction, 1 pregnancy, 1 hypertension, 1 presumed tuberculosis, 1 patient fatal pneumococcal sepsis and another serum sickness	See results	Population: Adult patients with HS. Comments: Authors reported that 17 patients experienced adverse events likely to be related to the immunogenicity properties of infliximab, and that 16/17 of these patient were receiving monotherapy. This is a systematic review although the inclusion and exclusion criteria are not clearly defined and there is a lack of definition of clinical efficacy. Largely case series and case studies utilised. Low level evidence study.

Appendix

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	None
Updated search terms - Population	Hidradenitis suppurat* Acne inversa
Updated search terms - Intervention	Infliximab Remicade Remsima Inflectra Monoclonal antibod*
Updated search terms - Comparator	Surg* Laser ablation* Cryotherapy Retinoid* Vitamin A Acitretin Isotretinoin Dapsone Immunosuppress* Ciclosporin anti*TNF alpha blocker*
Updated search terms - Outcome	None

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	Title/Abstract Publication date <5 yrs, <10 yrs RCTs, SRs, MAs English language
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	None