Systematic review of the efficacy and safety of biological therapy for inflammatory conditions in HIV-infected individuals

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**Introduction**

Biologic therapies are a class of protein drugs that target specific chemicals or cells in the human immune system. Most licensed biologic agents antagonise cytokines to treat a range of immune-mediated inflammatory diseases (Table 1). More than 90% of biologic therapies used for inflammatory conditions target tumour necrosis factor-alpha (TNF-α) (1). Like other biologic therapy targets, TNF-α has protean pro-inflammatory effects *in vivo*, such as inflammatory cell recruitment and release of additional cytokines interleukin-1 (IL-1) and IL-6 (2). Multiple therapeutic mechanisms have been employed to down-regulate its effects, including monoclonal antibodies that target TNF-α directly (e.g. infliximab), and neutralising soluble receptor antagonists (e.g. etanercept). These therapies have transformed care for HIV-negative populations with severe inflammatory conditions. Approximately 70% of anti-TNF-α agents used globally are prescribed for rheumatoid arthritis (3). In the UK approximately 6% of patients with rheumatoid arthritis (RA), over 12,000 individuals, receive biologic drugs. This is closer to 12% in The Netherlands and Spain where clinical thresholds for biologic therapy are lower (3).

While such agents dampen inflammation, they may also impair appropriate immune responses to infection, although the precise mechanisms are poorly understood (4,5). In light of this potential increased infection risk, HIV-infected individuals have not been included in randomised controlled trials of biologic therapies alongside elderly and other co-morbid patients that are thought to constitute nearly one third of current real-life biologic therapy use (6). Clinical data reporting use of biologic therapy for inflammatory disease in HIV-infected individuals are largely limited to case reports and case series. Literature reviews are limited to single specialty journals and do not cover the full spectrum of inflammatory conditions that affect HIV-infected individuals. There is a more substantial literature on use of biologic agents as chemotherapy for haematological malignancy in HIV-infected individuals (7).
In this article we review published data on the use of biologic therapies used to treat inflammatory conditions in HIV-infected individuals, focusing on, but not limiting discussion to, dermatological, gastroenterological and rheumatological indications. The paper also considers the clinical need for biologic therapy in the treatment of immune-mediated pathology in HIV-infected individuals. We address what might be extrapolated regarding efficacy and safety data from the biologic therapies literature of HIV-associated malignancy and HIV-uninfected populations.

Methods

The primary purpose of this systematic review was to provide an overview of all available studies of biologic treatments of non-malignant and non-lymphoproliferative inflammatory conditions in HIV-positive patients. The review focuses on dermatological, gastrointestinal, and rheumatological indications for biologic therapy. The range of biologic treatments examined was limited to those medications recommended by the National Institute for Health and Care Excellence (NICE) up to 1 July 2015, to pragmatically capture those therapies in current use. Since that date anakinra has been removed from RA treatment guidelines however the agent was included in our literature search. The study conduct was in accordance with the PRISMA statement for systematic reviews.

Search strategy:

Studies were extracted from search of online databases Embase and Medline (OvidSP) up to 1 July 2015. The search was restricted to adult articles from the English literature (Figure 1: Supplementary Material: Additional file 1: Search Strategy).

Initial screening of the titles and abstracts excluded animal studies, basic science studies, duplicate publications, and identified studies primarily on biologic therapy for inflammatory disease in HIV-infected individuals. The full texts of the remaining 52 articles were assessed by two authors for eligibility. Thirty-seven
papers were collected for final review. All English language case reports, case series and both prospective and retrospective observational studies were included. References, guidelines and expert opinion were consulted for additional information.

Results

Clinical need is poorly defined in HIV-infected individuals. Prevalence data on inflammatory conditions in HIV-infected populations are based largely on case reports, case series and single-centre studies. These heterogeneous data are further limited by the variable application of standardised disease classifications (8). This may be due to the absence of specific diagnostic tests or the lack of collaboration with specialty physicians (9). The natural history of inflammatory diseases in HIV-infected individuals is also complex. Onset of inflammatory pathology may be HIV-associated or independent of HIV infection, either preceding or postdating HIV acquisition. Case reports describe occult inflammatory disease unmasked both by HIV-mediated immunosuppression (10) and paradoxically after restitution of the immune system by initiation of antiretroviral therapy (ART) (11,12). Inflammatory manifestations associated with, or intrinsic to, HIV infection are well recognised and may mimic recognised conditions, in particular rheumatologic manifestations (13). Describing the confounding effect of HIV infection and ART on any of these processes is complicated and there are no comprehensive long-term prospective data (9). Despite this paucity of information inflammatory conditions are considered common in HIV-infected individuals with possibly different disease courses compared with HIV-uninfected populations.

Specific inflammatory conditions in HIV-infected individuals

Rheumatologic symptoms are common in HIV-infected individuals. In a large retrospective analysis of North American inpatients, arthritis or arthralgia was reported in 5.5% of HIV-infected individuals (13). High positive rates of non-specific autoantibodies, such as antinuclear antibodies (ANA) and rheumatoid factor (RF), were described in HIV-infected individuals in studies prior to ART
(14), however seroprevalence after initiating modern ART regimens are thought to be comparable to rates in the general population (15). Pre-ART era data suggested that rheumatoid arthritis and HIV-infection were mutually exclusive: the decline in CD4+ T cells mitigating lymphocyte-mediated autoimmunity (16). This dogma may have significantly prejudiced the nomenclature of subsequent studies. Since the introduction of ART multiple case reports and case series describe new presentations of symmetrical polyarthritis clinically suggestive of Rheumatoid Arthritis. This may affect between 0.1% and 5% of HIV-infected populations, vary geographically, and presentation usually occurs after HIV suppression (9). Reveille et al have proposed that HIV arthritis represents a distinct self-limiting acute arthropathy affecting principally large joints (17). Ankylosing spondylitis, psoriatic arthritis and reactive arthritis occur in HIV infected populations although accurate prevalence and natural history studies are not available, with undifferentiated spondyloarthropathy commonly used as a unifying term (9).

HIV-associated psoriasis most commonly appears as abrupt widespread skin disease or as a severe exacerbation in patients with known psoriasis (18). Paradoxically, for pathology caused by T cell activation, psoriasis presentation is associated with increasing immunodeficiency (18). These mechanisms are poorly understood but may relate to the proportional increase in CD8+ T cells late in HIV infection that are thought to mediate skin disease (19). In advanced HIV infection, generalised skin failure is relatively more common as are coexistence of several psoriasis phenotypes (20). Unlike other inflammatory conditions in the setting of HIV infection, ART is included in formal guidance for treatment of HIV-associated psoriasis (21).

Of the inflammatory conditions considered in this review, there is least known about the relationship between HIV infection and inflammatory bowel disease. A recent review of the subject identified only 47 eligible patients for study across all relevant literature (22). A small retrospective case-control study suggested that HIV infection predicted lower relapse rates of all causes of inflammatory bowel disease over 18 years follow up (23). The authors speculated that impaired cell-mediated immunity may be responsible.
Non-biologic treatment of inflammatory conditions in HIV-infected individuals

We identified no randomised placebo-controlled trials evaluating safety and efficacy of any treatments for inflammatory conditions in HIV-infected individuals. The small randomized controlled studies of disease-modifying anti-rheumatic drug use in HIV-infected patients were conducted to evaluate their role as HIV therapies, they did not include patients with autoimmune diseases and the study durations were short (24–26). However, in patients with well-controlled HIV infection use of standard immunosuppression, including methotrexate for treatment of inflammatory disease, is supported with caution (9,21,27). Corticosteroids are widely used in HIV-infected individuals to treat inflammatory conditions. The metabolic and endocrine toxicity of these drugs should be monitored closely in all patients with HIV infection (28), in particular those patients receiving ritonavir-containing ART regimens, which may potently increase the action and duration of corticosteroids. Cushing’s syndrome has been reported following single injections of triamcinolone and methylprednisolone and these should not be co-administered (29).

Systematic review of biologic therapies for inflammatory conditions in HIV-infected individuals

Overview

The literature search identified two case series and 15 case reports of HIV-infected individuals receiving biologic therapy for inflammatory conditions. One further case report published after our original literature search was executed was also included (30). This represents 37 treatment episodes with 6 different biologic agents encompassing 10 inflammatory conditions (see Table 2). Two case reports describe the same individual patient over 12 years of follow up (31,32). Five treatment episodes were identified in a report of Spanish biologic registry data but no individual clinical details were available for detailed outcomes analysis (6). Only for individual patients with diagnoses of psoriasis, psoriatic arthritis and rheumatoid arthritis were more than two cases returned. Of 37 treatment episodes 33 (89%) entailed use of anti-TNF-\(\alpha\) agents.
For 25 individual patients with adequate clinical details, HIV acquisition preceded onset of inflammatory symptoms in seven, post-dated inflammatory symptoms in nine and in nine other patients the relative timing is unknown. Two individuals started and failed biologic therapy before HIV testing was performed (33,34). The psoriatic symptoms of both of these patients responded dramatically to ART. Besides different systemic diagnoses, the small group of patients described in the literature may also represent disparate inflammatory syndromes: individuals with recognised pre-existing inflammatory disease (35,36), occult inflammatory conditions unmasked by both HIV-mediated immunosuppression (33,37) and ART (31,32,38), and inflammatory symptoms intrinsically related to HIV infection (33,34,39). It is unknown whether these represent clinical entities that can be directly compared in a study of therapeutic efficacy.

Baseline CD4 lymphocyte count and HIV viral load values were available in all but two patients receiving biologic therapy for inflammatory conditions (Table 2). The median CD4 count prior to initiation of biologic therapy was 446 cells/μL. Two patients developed inflammatory symptoms with advanced HIV infection and CD4 counts of 50 cells/μL or less. Both received only two doses of biologic therapy (33,37). Twenty patients (20/25, 80%) were established on ART at the time of commencing biologic therapy and 15 of these individuals had an undetectable HIV viral load. Two individuals commenced ART during their treatment with biologic agents. Of those established on ART before or during biologic therapy, the precise regimen was only described in 13 individuals (13/22, 59%). Two ART regimen changes were reported during biologic therapy however these were not attributed to any interaction with the biologic agent. No negative immunological or virological outcomes were described across the available literature. However CD4 count and viral load monitoring was inconsistent and often infrequent across the literature.
In a case control study of HIV-tuberculosis co-infected individuals not yet started on ART, 16 study patients received 8 doses of etanercept over 4 weeks in conjunction with routine quadruple anti-tuberculosis therapy (40). The 42 CD4 count matched control patients were already receiving oral prednisolone as part of a separate trial. Even in the absence of ART only a single patient experienced a significant rise in their viral load, leading to cessation of etanercept at 2 weeks.

**Efficacy**

Treatment duration ranged from induction therapy of three doses to years of maintenance therapy with a median follow up of 13 months after initiation of biologic therapy. The methods of reporting treatment efficacy were variable. The largest case series of eight patients was designed as a “study of safety” and thus does not include any disease activity scores at baseline or after biologic therapy (38). In the remaining cases, specific disease activity scores were recorded at baseline and at least once after initiation of biologic therapy in only five out of 37 treatment episodes (13.5%). Remission was achieved in all five cases. Where specific disease activity scores were unavailable a range of informal descriptions were used. Table 3 summarises the response of inflammatory conditions to biologic therapy: ‘unresponsive’ implies failure to respond to therapy from induction, ‘partial’ implies therapy did not reach unspecified therapeutic targets, ‘transient’ implies therapy did reach therapeutic targets but failed to sustain response, and ‘good’ implies therapy reached and sustained therapeutic targets which might include remission (Table 3). Of all treatment episodes 20/37 (54%) demonstrated a 'good' primary response to treatment and only 4/37 (11%) were 'unresponsive'. Biologic therapy was stopped or switched in 14/37 (11%) treatment episodes. This rate is comparable with non HIV-infected populations (41). In these 14 instances, three were prompted by adverse events and 11 by efficacy. Etanercept accounted for 50% (7/14) of the biologic agents stopped. However Etanercept was also the most common biologic agent used across all conditions (43%, 16/37). Dosing information was available for 11 out of 37 treatment episodes (30%) and largely conformed to international guidelines.
Concurrent with biologic agents 18 patients (18/25, 72%) received other synthetic disease-modifying anti-rheumatic drugs (DMARDs), including steroid therapy (14 patients) and methotrexate (eight patients). Dosing and duration of these agents was very poorly reported.

**Adverse events**

Analysis of adverse events described in the literature search encompassed those 42 treatment episodes involving treatment of inflammatory conditions (including five patients from the Spanish biologic registry data and a total of 37 treatment episodes described in other papers) and 33 treatment episodes involving treatment of HIV-infected individuals with biologic agents as trial therapy for HIV infection or tuberculosis. For those individuals where the identity of the biologic agent was known, 94% were anti-TNF-α agents (66/70 treatment episodes).

**Infectious complications**

We identified three infection episodes requiring hospital admission that were attributed to biologic therapy: facial abscess, listeriosis, and “frequent polymicrobial infections” (37,38,42). This equates to three infectious episodes in the cumulative 50 patient-years of all biologic therapies reported in our review. This is similar to HIV-uninfected populations where relative risk of infection is reported for individual biologic agents. In the German Biologics Register RABBIT (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie) study the reported relative risk of serious infection is 2.70 for all infliximab treatment (20.59 episodes per 100 patient-years) (43). By comparison, for synthetic DMARDs in HIV-uninfected patients registry data suggests that the incidence of serious infection is 5.08 per 100 patient-years (4).

Given the very small case numbers, our review cannot categorically report any clear association between CD4 count at time of initiation of biologic therapy and increased incidence of infectious complications. The patient with “polymicrobial infections” had a baseline CD4 count of 50 cells/μL. No clinical detail is provided
on the nature of these infections. However, the only other patient with a CD4 cell count less than 200 cells/μL among patients treated for inflammatory conditions, with 29 cells/μL, did not develop any infectious sequelae.

Combined corticosteroid and DMARD use with anti-TNF therapy is associated with increased risk of infectious complications in HIV-uninfected cohorts: an odds ratio (OR) of 14.5 for combined therapy compared with 2.9 for anti-TNF monotherapy in HIV negative patients (44). All four patients identified in our review with any infectious complications attributed to biologic therapy received concomitant corticosteroid therapy. However seven other patients in our review who also received concurrent corticosteroid therapy developed no infectious complications. Corticosteroid dosing was not consistently reported.

Age greater than 50 years is associated with a threefold increased risk for serious infections in patients receiving anti-TNF therapies (44). Advancing age is an independent risk factor for *Listeria monocytogenes* infection in any setting (45). The case of neuroinvasive listeriosis occurred in a patient aged 69 years (42).

In HIV-uninfected patients, the highest incidence of infectious complications occurs within six months of starting biologic therapy (46). All infectious complications occurred within six months of initiating biologic therapy in our review. There is little discussion of antibiotic prophylaxis in the cases returned. However one individual received dapsone prophylaxis following pneumocystis pneumonia, despite a well-preserved CD4 cell count at time of biologic therapy initiation (38). In the trial of etanercept as adjuvant therapy for tuberculosis as described above, two patients, with a mean CD4 count of 394 cells/μL, were withdrawn after four doses of etanercept owing to increasing burden of acid fast bacilli in sputum samples (40). We did not consider this evidence of a serious adverse event nor clearly attributable to the biologic therapy. In this study there were no increased infectious complications in those 16 HIV-infected individuals receiving etanercept compared with the 42 HIV-infected control patients.

Non-infectious complications
Allergic reactions, all within the first four doses of therapy, were experienced by three HIV-infected individuals (35,38,47). Anaemia and acute anterior uveitis have been described as adverse events but no clinical detail was provided (36,38). In a recent meta-analysis of HIV-uninfected patients, biologic therapy was associated with a small increased risk of melanoma but not other malignancy. No malignant complications were identified in our systematic review. Two HIV-infected patients died during the course of biologic therapy for non-haematological indications. Both deaths occurred in patients receiving etanercept as trial therapy for non-inflammatory conditions (HIV and tuberculosis, respectively) and the cause of death, mesenteric atherosclerosis and pulmonary embolism, were not deemed to be related directly to anti-TNF-\(\alpha\) therapy (40,48).

**Discussion**

Across all organ systems autoimmune inflammatory pathology is thought to be common in HIV-infected individuals. However the understanding of the natural history of these diverse conditions in the setting of HIV infection, as well as long-term follow-up of their clinical manifestations is limited. Even for non-biologic treatment of HIV-infected patients living with inflammatory conditions there are only limited efficacy and safety data. Biologic therapies have already transformed the lives of HIV-uninfected patients with severe autoimmune conditions. For HIV-uninfected patients these agents are increasingly used by clinicians and may in the future be “gold standard” for first-line therapy, irrespective of disease severity. Therefore both current and future clinical parity for HIV-infected individuals diagnosed with inflammatory diseases warrants closer and more rigorous consideration of biologic therapy use.

Unfortunately, the available literature that specifically addresses the use of biologic agents in the treatment of HIV-infected individuals with inflammatory conditions is of poor quality. For some specific inflammatory diagnoses, such as ulcerative colitis, some available data are limited to single patient case reports. Psoriasis represents the most studied condition but only eight treatment episodes were identified in the literature. Although detailed disease scoring
systems were often absent, our review suggests that treatment responses were comparable to HIV-uninfected patients receiving biologic therapy. Publication bias towards positive outcomes is a legitimate concern given the small sample. Unsurprisingly there are no “control” data for inflammatory outcomes in HIV-infected individuals. Uncertainty also remains in terms of HIV control during biologic therapy. A single case-control study examining the use of biologic agents for treatment of HIV-tuberculosis co-infection in patients not receiving ART suggested that etanercept did not adversely affect HIV control. As there are no equivalent studies for individuals established on ART, suggesting biologic therapies do not adversely interact with ART currently lacks an evidence-base. However, no negative effects on ART therapy were identified in our review.

The higher quality literature pertaining to the use of biologics for haematological indications is limited, almost exclusively to rituximab, whereas guidelines for treatment of severe inflammatory conditions in HIV-uninfected groups is predicated largely on use of anti-TNF-α agents. Patients with haematological malignancy and lymphoproliferative disorders may also represent a relatively more immunocompromised cohort of patients and who receive concurrent chemotherapy, confounding direct comparison with patients receiving the same agents for inflammatory indications.

In summary, our systematic review highlights a paucity of good quality data on use of biologic therapies to treat inflammatory conditions in HIV-infected individuals. All evidence reviewed that addressed this clinical area directly rated very low quality according to the GRADE system (49). Due to this major limitation, the review of a cross-section of common inflammatory conditions and agents, we cannot conclude or exclude comparable efficacy and safety of biologic therapies between HIV-infected and –uninfected populations. However we feel that available data supports inclusion of HIV-infected individuals with well-controlled HIV infection in future studies of biologic therapy. There remains a broader need to study the diagnosis, natural history, and management of inflammatory conditions in HIV-infected populations. Rigorous and formal prospective data collection of this burgeoning group of patients would represent
a key first step to this better understanding (Table 4). This may lead to care
equality for HIV-infected patients suffering from inflammatory conditions who
might benefit from biologic therapies that continue to transform the lives of HIV-
uninfected individuals.

Epidemiology and Treatment of New-Onset and Established Rheumatoid
Arthritis in an Insured US Population. Arthritis Care Res. 2015
Dec;67(12):1646–55.

2. Kopf M, Bachmann MF, Marsland BJ. Averting inflammation by targeting the

3. Jönsson B, Kobelt G, Smolen J. The burden of rheumatoid arthritis and
access to treatment: uptake of new therapies. Eur J Health Econ HEPAC
Health Econ Prev Care. 2008 Jan;8 Suppl 2:S61-86.

et al. Infections in patients with rheumatoid arthritis treated with biologic

5. Wallis RS. Tumour necrosis factor antagonists: structure, function, and

6. García-Doval I, Carretero G, Vanaclocha F, Ferrandiz C, Daudén E, Sánchez-
Carazo J-L, et al. Risk of serious adverse events associated with biologic and
nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for

7. Castillo JJ, Echenique IA. Rituximab in combination with chemotherapy
versus chemotherapy alone in HIV-associated non-Hodgkin lymphoma: a

8. Lawson E, Walker-Bone K. The changing spectrum of rheumatic disease in


10. Siva C, Brasington RD. Worsening of arthritis with antiretroviral therapy:
the coexistence of rheumatoid arthritis and human immunodeficiency virus

11. Calabrese LH, Kirchner E, Shrestha R. Rheumatic complications of human
immunodeficiency virus infection in the era of highly active antiretroviral
therapy: emergence of a new syndrome of immune reconstitution and


49. GRADE handbook [Internet]. [cited 2016 Sep 19]. Available from: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.z014s19g02b2