The role of biological agents in the management of large vessel vasculitis: a comprehensive systematic review

Mohammed Osman, Christian Pagnoux, Dale Storie, Joanne Homik and Elaine Yacyshyn

Research Protocol

Background

Vasculitides are a group of rare heterogeneous autoimmune conditions where inflammation is present within the walls of blood vessels. These conditions may be primary in origin (where no other cause is attributed to their pathogenesis) or secondary to systemic infections, underlying malignancy or other connective tissue diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, scleroderma, ankylosing spondylitis, or scleroderma) (reviewed in 1). Traditionally, vasculitides were classified according to the sizes of the vessels affected 2,3. Using this method, primary large vessel vasculitides (LVV) include Giant Cell Arteritis (GCA, Horton’s disease, Temporal Arteritis) and Takayasu’s arteritis (TA) which primarily affect the aorta and its major branches 3-6.

GCA is the most common primary vasculitis in adults. It usually involves extracranial branches of the carotid artery (e.g. temporal artery), although the aorta is also often involved. According to the original American College of Rheumatology (ACR) the diagnosis of GCA is very likely (sensitivity > 93 %, specificity > 91 %) if the presence of three or more of the following five criteria are present: age over 50, new onset headache, temporal artery tenderness or decreased pulsation, erythrocyte sedimentation rate ≥ 50 mm/h, or an abnormal temporal artery biopsy 5. Although an abnormal temporal artery biopsy aids in the diagnosis, a normal one does not exclude it 7. In addition to the involvement of branches of the external carotid artery, other branches of the aorta may be involved in GCA which may result in limb ischemia, or vessel aneurysms 8. The current initial treatment for GCA requires prompt daily doses of corticosteroids for a prolonged course in order to avert irreversible visual loss, aneurysms in the branches of the aorta or limb ischemia.

TA, like GCA, also involves the branches of the aorta. Patients with TA, like GCA, often have similar symptoms (jaw claudication, headaches, weakness, diplopia) 9. Although the underlying pathophysiology of TA is not clear, like GCA it appears to be T cell mediated 10. In fact, these two diseases may not be different entities, but rather different phenotypes of the same disorder 9. Unlike GCA, TA results in the formation of granulomatous lesions within blood vessels which may result in vessel stenosis, occlusion, dilatation and/or vessel aneurysms. In addition, TA is associated with vessel occlusions which may pose life/limb threatening ischemic events if not promptly treated. According to the ACR, the diagnosis of TA is accepted (> 90 % sensitivity, 97 % specificity) when three out of the following six criteria (with one criterion showing anatomical abnormalities) are met: age < 40, claudication of one or more extremities
(upper limb), decreased brachial artery pulse, systolic BP difference > 10 mm between arms, bruits over subclavian arteries or aorta, and arteriographic narrowing of the aorta, its primary branches, or large arteries in the proximal upper or lower extremities not secondary to arteriosclerosis or fibro-muscular dysplasia. Like GCA, prompt treatment of patients with TA using glucocorticoids is essential; however, unlike GCA, many patients with TA are difficult to control once glucocorticoids are stopped.

**Rationale**

The accepted initial therapies for patients with GCA or TA are glucocorticoids. Besides the various morbidities associated with the prolonged use of glucocorticoids, many patients with both GCA and TA are resistant to glucocorticoid therapies. Although other immunosuppressive reagents such as disease modifying agents used in other autoimmune conditions, or anti-cytokine/immune cell monoclonal antibodies (biological agents) have become widely available, they are often employed with variable efficacies for the management of patients with GCA and TA that are refractory to glucocorticoid therapy. The purpose of this systematic review is to critically appraise and summarize all the available evidence for the use of non-glucocorticoid medical therapies, particularly on the biological agents in the management of GCA and TA.

**Study Questions**

1. Evaluate the role of biological agent therapies ((tumor necrosis factor alpha inhibitors (infliximab, etanercept, adalimumab), anti-interleukin 6 agents (tocilizumab), anti-CD20 (rituximab), anti-interleukin 12/23 (ustekinumab), anti-CTLA4 (abatacept)) in inducing and/or maintaining remission in patients with GCA or TA.
2. Evaluate the role of these agents in stopping/reducing concurrent glucocorticoids.

**Searches and Databases**

No restrictions on language, or publication period.

With the assistance of a medical librarian, the following databases will be searched: Medline, EMBase, Proquest (for theses) and the Cochrane Library (EBM reviews). A manual search of abstracts presented at the annual meetings of the Canadian Rheumatology Association (CRA), European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), and clinicaltrials.gov from 2009 to 2012 will be performed.

Search strategy:

**Medline** (Ovid 1946 – present)

MeSH terms: (vasculit* or arterit*) and large vessel).mp; (giant cell or temporal or cranial or granulomatous) adj1 (arterit** or aortiti*) or (horton* adj1 disease*).mp; (takayasu* or aortitis).mp; takayasu arteritis/dt; aortitis/dt; infliximab.mp; adalimumab.mp; etanercept.mp;
tocilizumab.mp; methotrexate.mp; azathioprine.mp; exp Mycophenolic Acid/ or mycophenolate mofetil.mp; rituximab.mp; remicade.mp.; humira.mp; enbrel.mp; actemra or roactemra).mp; (Abitrexate or Folex or Mexate or Rheumatrex or Trexall or Metoject or Rheumatrex or Ebetrex).mp; (Azasan or Imuran).mp; (cellcept or myfortic).mp; (rituxan or mabthera).mp; exp Antibodies, Monoclonal/exp Antirheumatic Agents; leflunomide.mp.; arava.mp; Isoxazoles; exp Cyclophosphamide/cyclophosphamide.mp; Cytoxan or Neosar or Endoxan or Procytox).mp; abatacept.mp; orenencia.mp; ustekinumab.mp; stelara.mp; Tumor Necrosis Factor-alpha/ai; exp anti-inflammatory agents, non-steroidal; exp CTLA-4 Antigen/ai [Antagonists & Inhibitors]; ((tnf alpha or tumor necrosis factor alpha) adj2 (inhibitor* or anti)).mp; exp Immunosuppressive Agents.

**EMBASE** (1974 – present)

MeSH terms: (vasculit* or arterit*) and large vessel).mp; (((giant cell or temporal or cranial or granulomatous) adj1 (arterit** or aortiti*)) or (horton* adj1 disease*)).mp; (takayasu* or aortitis).mp; infliximab.mp.; adalimumab.mp; etanercept.mp; tocilizumab.mp; methotrexate.mp; azathioprine.mp; exp Mycophenolic Acid/ or mycophenolate mofetil.mp; rituximab.mp; remicade.mp; humira.mp; enbrel.mp; (actemra or roactemra).mp; (Abitrexate or Folex or Mexate or Rheumatrex or Trexall or Metoject or Rheumatrex or Ebetrex).mp; (Azasan or Imuran).mp.; (cellcept or myfortic).mp.; (rituxan or mabthera).mp; leflunomide.mp; arava.mp; Isoxazoles/exp; Cyclophosphamide/cyclophosphamide.mp; (Cytoxan or Neosar or Endoxan or Procytox).mp; abatacept.mp; orenencia.mp; ustekinumab.mp; stelara.mp; ((tnf alpha or tumor necrosis factor alpha) adj2 (inhibitor* or anti)).mp; exp *monoclonal antibody.

**EBM Reviews - includes the following databases:**


MeSH terms: ((vasculit* or arterit*) and large vessel).mp; (((giant cell or temporal or cranial or granulomatous) adj1 (arterit* or aortitis)) or (horton* adj1 disease*)).mp; (takayasu* or aortitis).mp.

**Web of Knowledge** - (includes Science Citation Index and Science Conference Proceedings)

Topic=(("giant cell arteritis" OR "large vessel vasculitis" OR takayasu OR "temporal arteritis" OR "horton disease").

AND
Topic=(infliximab or adalimumab or etanercept or tocilizumab or methotrexate or azathioprine or mycophenol* or rituximab or remicade or humira or enbrel or actemra or roactemra) OR Topic=(abitrexate or folex or mexate or rheumatrex or trexall or metoject or rheumatrex or ebetrex or azasan or imuran or cellcept or myfortic or rituxan or mabthera or leflunomide or
arava or isoxazoles or cyclophosphamide or cytoxan or neosar or endoxan or procytox or abatacept or orencia or ustekinumab or stelara or "tnf alpha inhibitor" or "tnf alpha antagonist" or "anti tnf" or "anti tumor necrosis factor" or "tumor necrosis factor alpha inhibitor" or "tumor necrosis factor alpha antagonist").

**Types of studies included and excluded**

**Included:** case-control studies, randomized control studies (both blinded and non-blinded), observational cohort studies, case series with all GCA and/or TA patients receiving the described biological /disease modifying immunosuppressive agents for the induction/maintenance of remission. The reason why disease modifying agents are included in the search is to capture patients treated with these agents and biological agents concomitantly.

**Excluded:** case reports and all case-control studies, randomized control studies, observational cohort studies, case series not using disease remission or maintenance of disease remission as a primary outcome, and studies using non-steroidal immunosuppressive agents without any biological agents.

After conducting the search using the above criteria, identified studies will be reviewed by two independent reviewers (M. Osman and E. Yacyshyn) to determine whether they are eligible to be included or excluded in the study. Differences in choices will be resolved by consensus.

**PICO**

**Patients with Giant Cell Arteritis**, all patients, no age limits.

**Patients with Takayasu’s Arteritis**, all patients, no age limits.

**Intervention(s), exposure(s):** Biological agents (etanercept, infliximab, adalimumab, abatacept, rituximab, ustekinumab) and disease modifying immunosuppressive agents (cyclophosphamide, azathioprine, leflunomide, methotrexate, mycophenolate mofetil).

**Comparator(s) – induction and maintenance of remission, reduction/elimination of concomitant glucocorticoids.**

**Primary outcome**

Induction of disease remission in GCA or TA.

- Disease remission for GCA is defined as normalization of symptoms (no fever (< 38°), headache, visual, jaw/limb claudication), ESR < 25 mm/h, CRP < 10, and/or use of < 10 mg/d of prednisone or its steroid equivalent.
- Disease remission in TA is defined as normalization of symptoms (weakness, limb claudication, fever (as previously defined)), presence of pulses in all limbs, no new
bruits, ESR < 25 mm/h, CRP < 10 and improved/stabilized vascular lesions on vascular imaging (MRA, CTA or PET/CT).

**Secondary outcomes**

Mean glucocorticoid dose at remission, adverse effects and relapses/flare.

Relapse/flare is defined as any escalation of therapy, or use of prednisone dose > 10 mg/d, return of symptoms (as described above). In addition, TA patients may also have a relapse with the presence of a new bruit on exam, or loss of a pulse in any extremity.

Severe complications include any medical conditions related to the disease (e.g. myocardial infarction, intestinal/limb ischemia, visual loss) or immunosuppression (i.e. infections or severe neutropenia) requiring hospital admission.

**Extracted data**

In addition to primary and secondary outcomes, the following data will be extracted when available:

Type of study, duration of disease prior to biological agent, number of patients in each study, median age (yrs) for each study, gender (female ratio), disease modifying non-glucocorticoid immunosuppressive medications (both ongoing and used at the time of intervention), value of inflammatory markers (ESR and CRP) prior to and after biological agent interventions.

**Risk of bias (quality) assessment**

For case control studies, cohort studies and case series, a modified New-Castle Ottawa scale will be used to assess quality and validity of included studies. Randomized trials will be assessed using the Jadad or Oxford quality scoring system.

**Analysis**

Using a narrative description, every selected study will be analyzed to determine whether the primary outcomes have been reached using different biologic agents for GCA or TAA. Specifically, the percentage of patients achieving remission, the median corticosteroid dose at the initiation of biological agent therapy and at remission, and the risk of relapse will be determined for every study. Also, the adverse effects for each study will be compiled and added to the narrative analysis.
References


