Autoimmunity Reviews xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Non-glucocorticoid drugs for the treatment of Takayasu's arteritis: A systematic review and meta-analysis

Lillian Barra [a,*], Grace Yang [a], Christian Pagnoux [b], The Canadian Vasculitis Network (CanVasc)

[a] Department of Medicine, Division of Rheumatology, University of Western Ontario, London, Canada
[b] Vasculitis Clinic, Division of Rheumatology, Mount. Sinai Hospital, University of Toronto, Toronto, Canada

ARTICLE INFO

Article history:
Received 16 January 2018
Accepted 22 January 2018
Available online xxxx

Keywords:
Takayasu's arteritis
Large vessel vasculitis
Treatment
Biologics
Immunosuppressant

ABSTRACT

Background: Takayasu's Arteritis (TAK) affects mostly young women and causes significant morbidity. Most patients are refractory to glucocorticoids (GC) or relapse when GC doses are reduced. The objective of this study is to summarize the literature pertaining to the effectiveness of non-GC drugs for the treatment of TAK.
Methods: MEDLINE and Embase were searched for English-language studies of TAK patients with a sample size >5. Studies were included if the effectiveness of non-GC drugs for the treatment of TAK was reported. Random effects meta-analyses of various effect measures were performed.
Results: Of the 915 studies identified by the search, 14 of small molecule immunosuppressants (IS) and 25 of biologic therapies were included. Studies had a high risk of bias. Pooled remission rates were similar for both categories of non-GC drugs: 58% (95% CI: 40–74%) and 64% (95% CI: 56–72%), respectively. The relapse rate was 54% (95% CI: 39–68%) for IS therapies and 31% (95% CI: 22–41%) for biologics. Both significantly decreased GC doses and acute phase reactants. Observational studies suggested that anti-TNF agents were more effective than IS at maintaining remission. Randomized-controlled trials (RCTs) of biologics were of small sample size: abatacept was not effective and the trial of tocilizumab was underpowered to detect a difference in time to relapse versus placebo. Serious adverse events were uncommon.
Conclusions: Non-GC agents were moderately effective in inducing remission in TAK, but relapse rates were high. Larger, better designed studies are required to determine the optimal treatment regimen for TAK.

Contents

Abbreviations: AZA, azathioprine; ADA, adalimumab; CYA, cyclosporine A; CYX, cyclophosphamide; ETN, etanercept; FK, tacrolimus; IFX, infliximab; IS, immunosuppressant; LFM, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; TAK, Takayasu's Arteritis; TCZ, tocilizumab; TNF, anti-tumor necrosis alpha drug.

* Corresponding author at: St. Joseph's Health Care, 268 Grosvenor St., Room D2-160, London N6A 4V2, Ontario, Canada.
E-mail address: lillian.barra@sjhc.london.on.ca (L. Barra).

https://doi.org/10.1016/j.autrev.2018.01.019
1568-9972/

1. Introduction

Takayasu's Arteritis (TAK) is a rare large vessel vasculitis characterized by granulomatous inflammation of the aorta and its major branches causing claudication symptoms and potentially severe ischemic complications with major organ dysfunction [1]. TAK predominantly affects women and onsets before the age of 40, including children [2]. The disease is chronic, continuous or following a remitting-relapsing pattern, with decades of morbidity, disability and poor quality of life [3]. Mortality is 3 times higher than the general population [4]. The first-line treatment for active TAK is systemic glucocorticoids (GC), usually started at high doses followed by a tapering regimen [5,6]. Unfortunately, most patients either fail to achieve remission with GC or relapse on lower doses [7,8]. In addition, chronic GC therapy is associated with common and potentially severe adverse effects, such as infections, osteoporosis, cardiovascular disease, and growth restriction in children. For these reasons, effective treatment with small molecule immunosuppressants (IS) and/or biologic therapies would be highly beneficial [7,8].

There are no strong data available to date that favour one such drug over others that have been tried for the management of TAK [9]. Most evidence comes from small observational studies and case series. Consequently, the choice of any such non-GC therapy in TAK is often based on physicians' familiarity, patients' preferences, and trial-and-error. The primary goal of the present meta-analysis was to quantify the effectiveness of currently available non-GC treatments for TAK. Specifically, the outcomes of interest were (1) the proportion of patients with TAK achieving remission, (2) the proportion of patients with TAK with relapse over the follow-up period, (3) the magnitude of decrease in daily GC dose, (4) the magnitude of decrease in acute phase reactants (APR), and (5) the impact on imaging progression.

2. Methods

2.1. Literature search and study selection

The literature review was conducted using Embase and MEDLINE covering the period from database inception to January 2018. The search included terms for TAK and non-GC drugs (small molecule IS and biologic therapies) (Table A.1). Studies enrolling adult and pediatric-onset TAK patients reporting the effectiveness of steroid-sparing agents were included. Studies that included patients with other types of vasculitis in addition to TAK were only included if outcomes were reported separately for TAK. Case reports, case series with <5 subjects and non-English language papers/abstracts were excluded. If there were multiple studies of the same cohort with the same outcomes, the largest study was included. Two authors (LB and GY) independently reviewed the studies for inclusion and exclusion criteria.

2.2. Data extraction and quality assessment

Data extraction was performed by LB and GY independently using standardized forms. The following data were extracted: study design, age of study subjects and disease duration at study onset, gender, duration of follow-up, doses of steroid-sparing agents, duration of treatment, outcomes for drug effectiveness/efficacy and adverse events. Treatments were separated into two major categories: (1) small molecule steroid-sparing IS (cyclophosphamide (CYX), methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), leflunomide (LFM), cyclosporine A (CSA), tacrolimus (FK), or others) and (2) biologic therapies (anti-tumor necrosis factor alpha (anti-TNF): infliximab (IFX), etanercept (ETN), adalimumab (ADA), certolizumab (CZP) or golimumab (GOL), tocilizumab (TCZ, anti-IL6), abatacept (ABA, anti-CTLA4) and rituximab (RTX, anti-CD20)). For consistent reporting of outcomes, Hozo's method to estimate mean and standard deviation based on median, range and sample size was used [10]. The quality of observational studies was assessed using the Newcastle-Ottawa score [11] and of RCTs using the Cochrane Risk of Bias tool [12].

2.3. Meta-analysis

Outcomes varied widely across studies. Random effects meta-analyses (DerSimonian and Laird method) were performed for the most commonly reported outcome measures: proportion of patients achieving remission, proportion relapsing or experiencing disease progression on imaging, change in prednisone dose, Erythrocyte Sedimentation Rate (ESR) or C-reactive protein (CRP). Composite disease activity scores were inconsistently reported in studies and not included in this meta-analysis. Small molecule and biologic therapies were analyzed separately; anti-TNF and tocilizumab were analyzed both separately and together. There were too few RCTs to include in the meta-analyses; results of these studies were described in the systematic review.

The included studies defined remission as complete resolution of clinical symptoms and physical exam findings of TAK and no evidence of disease activity by acute phase reactants (ESR or CRP). Most studies also included stable or improved imaging in their definition of remission. Relapses were defined as new or recurrent TAK symptoms and/or elevations in APR attributable to TAK as determined by the treating physician and/or disease progression on imaging. Details regarding the imaging modalities used, timing of the exam and specific imaging findings that were deemed to be indicative of active disease were inconsistently reported. Heterogeneity between studies was reported using the I^2 and publication bias was assessed using funnel plots. All analyses were performed using Comprehensive Meta-Analysis (Biostat, Englewood, NJ). The design and conduction of this systematic review and meta-analysis followed the PRISMA statement [13].

3. Results

3.1. Search results and characteristics of included studies

Database searches identified 915 studies and 775 did not meet inclusion criteria as determined by title and abstract review. After full article review, an additional 96 studies were excluded due to lack of outcomes of interest and 9 due to low sample size of <5. In total, 35 observational studies [7,8,14–43] and 4 randomized controlled trials (RCTs) [44–47] were included in the systematic review (Fig. A.1).

The characteristics of the observational studies are shown in Table 1. Twelve studies investigated small molecule IS: 2 CYX [14,15], 5 MTX [15–18,48], 1 AZA [19], 2 MMF [20,21], 1 LFM [22] and 2 with various drugs included but reported separately [7,8]. Twenty-three studies investigated biologics: 12 anti-TNF [8,23–31,33,48], 9 TCZ [35,36,38–41,49], 1 RTX [42] and 2 both anti-TNF and TCZ reported separately [32,34]. All patients were treated with concomitant GC. For most studies, patients had been previously exposed to at least 1 other non-GC drug. Anti-TNF agents were frequently used in combination with MTX or AZA. The sample sizes ranged from 5 to 235 with the largest study consisting of 161 patients treated with MMF, 54 with AZA and 20 with MTX [7]. The ages of study subjects at the time of study enrolment ranged from 3 to 61 and 67–100% were females. The disease duration of subjects at the time of study enrolment varied widely across studies from new onset disease up to a median of 116 months. The duration of follow-up in the studies ranged from a median of 6 to 71 months. Using the Newcastle-Ottawa Score, the studies were of low or unclear quality: risk of selection bias was high or derivation of the cohort was not described, only two of the studies included a comparator group (and analyses did not account for confounders), blinding of outcome assessments was not performed or not reported and many studies did not adequately account for all participants at follow-up.

There were 4 double-blind placebo-controlled RCTs included: 1 curcumin ($N = 246$) [44], 1 resveratrol ($N = 220$) [45], 1 TCZ ($N = 36$) [47] and 1 ABA ($N = 26$) [46](Table 2). The age of participants ranged

Please cite this article as: Barra L, et al, Non-glucocorticoid drugs for the treatment of Takayasu's arteritis: A systematic review and meta-analysis, Autoimmun Rev (2018), https://doi.org/10.1016/j.autrev.2018.01.019