Pharmacologic Management of Takayasu's Arteritis: a Systematic Review

Grace Yang[1], Kevin Lee[1], Christian Pagnoux[2], Lillian Barra[3], CanVasc

[1]Schulich School of Medicine & Dentistry, Dept of Internal Medicine, University of Western Ontario, [2]Rheumatology, Mount Sinai Hospital, University of Toronto; [3]Rheumatology, St. Joseph's Health Care, London, ON, Canada

Introduction

- Takayasu's arteritis (TAK) is a large vessel vasculitis characterized by granulomatous inflammation, involving the aorta and its major branches.
- A large proportion of TAK patients are glucocorticoid-resistant with frequent relapses

Objectives

To review the evidence on immunosuppressants and biologic therapies for the treatment of TAK

Methods

- Literature review conducted using Embase, Medline, Cochrane databases and European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) annual meeting abstracts, from 1947 to July 2015.
- Search terms: TAK, treatment, drug therapy, and all possible immunosuppressants and biologics.
- Case reports and small case series (< 4 cases) were excluded. Only treatment specific outcomes were included.
- Two authors independently reviewed the articles

Results

Figure 1. Search results

915 articles

805 excluded for irrelevance

46 cohort studies excluded as outcomes were not reported according to treatment received

29 case series excluded for sample size <4

35 articles fit inclusion criteria

Results

Immunosuppressants

Table 1. Characteristics of Studies Investigating the effectiveness of Immunosuppressants for the Treatment of TAK

	Study	Study design	N	Mean age	% female	Disease duration (mo)	Previous IS	Follow-up (mo)
Cyclophosphamide								
1	Shelhamer et al 1985	prospective	7	26.7	100%	n/a	No	55.2
2	Chopra et al 1988	prospective	8	30	88%	n/a	n/a	n/a
Methotrexate								
3	Leavitt et al 1994	prospective	16	30	83%	62.4	No	33.6
4	Gokhale et al 2013	Prospective	36	22.86	83%	20.92	No	24
Azathioprine								
5	Valsakumar et al 2003	prospective	15	28.3	100%	12.9	No	12
Mycophenolate mofetil								
6	Goel et al 2010	retrospective	21	31.9	91%	35.5	No	9.6
7	Shinjo et al 2007	prospective	10	29.9	70%	57.5	Yes	36
Leflunomide								
8	De Souza et al 2012	prospective	15	36.2	93%	38	Yes	9.1

Table 2. Outcomes of Studies Investigating the effectiveness of Immunosuppressants for the Treatment of TAK

	Outcome	% Reduction in prednisone	ESR (% change)	CRP (% change)
Cyclophosphamide				
1	No mortality	n/a	n/a	n/a
2	100% myocardial improvement	n/a	n/a	n/a
Methotrexate				
3	81% complete remission	n/a	n/a	n/a
4	96% decrease in mean ITAS	n/a	-56%	-68%
Azathioprine				
5	100% absence of symptoms	n/a	-63%	-90%
Mycophenolate mofetil				
6	86% decrease in mean ITAS	47%	-36%	-53%
7	90% inactive disease	76%	-48%	-53%
Leflunomide				
8	80% inactive disease	59%	-7%	-49%

Summary Table 1/2

- Small studies of young females with no prior IS treatment
- Variable disease duration and follow-up
- 80-100% response rate
- Variable reporting of steroid sparing effect (50-70% lower) and ESR/CRP (most >50% decrease)

Biologic agents

Table 3. Characteristics of Studies Investigating the effectiveness of Biologic Agents for the Treatment of TAK

	Study	Study design	N	Mean age	% female	Disease duration (mo)	Previous IS	Follow-up (mo)
anti-TNF								
9	Mekinian et al 2011	retrospective	15	41	87%	37	Yes	43
10	Hoffman et al 2004	prospective	15	27.5	93%	6.5	Yes	21.7
11	Schmidt et al 2012	retrospective	20	33	95%	15.9	Yes	54
12	Molloy et al 2008	retrospective	25	35	88%	116	Yes	28
13	Serra et al 2014	prospective	5	36	80%	n/a	No	34
14	Comarmond et al 2012	case series+review	84	28.5	89%	24	Yes	10
15	Karageorgaki et al 2007	case series	4	25	100%	n/a	Yes	n/a
16	Novikov et al 2013	case series	9	29	100%	74	Yes	n/a
17	Filocamo et al 2008	retrospective	4	11	75%	n/a	Yes	n/a
18	Tombetti et al 2013	retroseptive	15	36	100%	n/a	Yes	46
19	Quartuccio et al 2012	retrospective	15	n/a	n/a	n/a	n/a	71
20	Kostina et al 2011	case series	5	n/a	100%	4.5	Yes	n/a
21	Boccacci et al 2011	retrospective	7	11.9	88%	12.5	Yes	58.8
22	Schiavon et al 2013	propsective	4	23	100%	67.75	Yes	44.3
Tocilizumab								
23	Nakaoka et al 2013	propsective	4	29	75%	3.8	Yes	n/a
24	Goel et al 2013	retrospective	10	24.5	90%	25.5	Yes	8
25	Canas et al 2014	retrospective	8	31	100%	4.5	Yes	18.5
26	Abisror et al 2013	case series + review	44	26	n/a	n/a	n/a	15
27	Tombetti et al 2013	retrospective	7	n/a	100%	66	n/a	14
28	Yamazaki et al 2013	prospective	6	12.5	n/a	94	Yes	n/a

Table 4. Outcomes of Studies Investigating the effectiveness of Biologic Agents for the Treatment of TAK

	Complete remission[a]	Response	% Reduction in prednisone	ESR (% change)	CRP (% change)
anti-TNF					
9	n/a	80% inactive disease	70%	-87%	-70%
10	67%	27% partial remission	100%	n/a	n/a
11	90%	n/a	n/a	n/a	n/a
12	44-57%[b]	22-29%[b] partial remission	100%	n/a	n/a
13	n/a	88% decrease in mean VAS	n/a	-84%	-87%
14	37%	53% partial remission	80%	n/a	n/a
15	75%	n/a	n/a	n/a	n/a
16	56%	86% decrease in ITAS, 33% partial remission	75%	-75%	-94%
17	50%	50% partial remission	n/a	n/a	n/a
18	53%	73% inactive disease, 33% partial remission	56%	-33%	-64%
19	n/a	25% decrease in mean BVAS	75%	n/a	n/a
20	n/a	100% absence of symptoms	n/a	n/a	n/a
21	71%	n/a	n/a	n/a	n/a
22	75%	n/a	n/a	n/a	-97%
Tocilizumab					
23	100%	n/a	93%	n/a	-97%
24	60%	100% decrease in mean ITAS	78%	-81%	-48%
25	n/a	100% improvement based on VAS and symptoms	88%	n/a	n/a
26	n/a	signifiant improvement in disease activity	n/a	-90%	-100%
27	43%	14% partial remission	0%	n/a	n/a
28	n/a	100% improvement of symptoms	77%	-91%	n/a

[a] definition is variable amongst studies. [b] outcomes reported separately for each anti-TNF studied (etanercept and infliximab). Prospective study = prospective open-label study. IS: immunosuppressant; VAS: visual analog scale; ITAS: Indian Takayasu Activity Score; BVAS: Birmingham Vasculitis Activity Score; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein

Conclusions

- There are no controlled trials of pharmacologic therapies in TAK
- Due to heterogeneity of studies, a meta-analysis could not be done, and comparisons between various treatment options cannot be made
- Various immunosuppressants have been shown in small prospective and retrospective studies to be effective in inducing and maintaining remission in combination with glucocorticoids;
- Anti-TNF and Tocilizumab have been shown to provide benefit intreating patients who have relapsed or become steroid-dependent on conventional immunosuppressants
- Given the rarity of disease, multi-national randomized controlled trials are needed to determine the efficacy of available immunosuppresants and biologic therapies for treating TAK

Summary Table 3/4:

- Wide variation in disease duration; most resistant to multiple IS treatments
- Wide variation in outcome measurement- difficult to meta-analyze or compare data
- Anti-TNF: 40-90% complete remission
- Tocilizumab: 40-100% complete remission
- All were steroid sparing by 50-100% of initial dose
- All associated with significant decrease in ESR/CRP

Acknowledgement

Special thanks to CIORA for funding