Summary tables of evidence SLR focused on treatment – results on GCA

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LIST OF ABBREVIATIONS

ACEI: angiotensin-converting enzyme inhibitors

ACR: American College of Rheumatology

ACTH: Adreno Cortico Tropic Hormone

AE: adverse event(s)

ABA: abatacept

ADA: adalimumab

ADR: adverse drug reaction

AION: anterior ischaemic optic neuropathy

APR: acute phase reactants

ARB: angiotensin receptor blockers

ASA: acetylsalycilic acid

AZA: azathioprine

bDMARDs: biologic disease-modifying anti-rheumatic drugs

BAL: bronchoalveolar lavage

Hb: haemoglobin

HR: hazard ratio

IBD: inflammatory bowel disease

ICU: intensive care unit

IGRA: interferon gamma release assay

BP: blood pression

BSR: British Society for Rheumatology

BVAS: Birmingham vasculitis activity score

CDS: colour duplex sonography

CKD: chronic kidney disease

CMV: cytomegalovirus

CsA: cyclosporine

csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs

CRP: c-reactive protein

CTA: computed tomography angiography

CT: computed tomography

CVD: cardiovascular disease

DEXA: dual-energy x-ray absorptiometry scan

DMARD: disease-modifying anti-rheumatic drugs

MSK: musculoskeletal

MRA: magnetic resonance angiography

MR: modified release

MRI: magnetic resonance imaging

Nsp: not specified

DM: diabetes mellitus

Dx: diagnosis

ESR: erythrocyte sedimentation rate

ETA: etanercept

FDG: fluorodeoxyglucose

FU: follow-up

GC: glucocorticoids (prednisone if not otherwise specified)

GCA: giant cell arteritis

GI: gastrointestinal

GFR: glomerular filtration rate

HAQ: health assessment questionnaire

HBV: hepatitis B virus

HCQ: hydroxychloroquine

HCV: hepatitis C infection

PT: patient

PTA: percutaneous transluminal angioplasty

Pts: patients

p.o.: per os

PPI: proton pump inhibitor

IQR: interquartile range

IR: incidence rate

i.v.: intravenous

IL-6: interleukin 6

IFX: infliximab

Lab: laboratory abnormalities

LEF: leflunomide

LFTs: liver function tests

LVV: large vessel vasculitis

LV-GCA: large vessel giant cell arteritis

MMF: mycophenolate mophetil

Mo: months

MTX: methotrexate

TIA: transient ischaemic attack

TNF: tumour necrosis factor

TST: Mantoux tuberculin skin test

TNFi: tumour necrosis factor inhibitors

Tx: therapy

US: ultrasound

UST: ustekinumab

N: number

Na: not applicable

Neg: negative

NIH: National Institute of Health

Ns: not significant statistical result

Nsp: not specified

NSAIDs: non-steroidal anti-inflammatory drugs

OP: osteoporosis

PCP: pneumocystist jiroveci pneumonia

PET-CT: Positron emission tomography-computed tomography

PET: positron emission tomography

PION: posterior ischaemic optic neuropathy

PMR: polymyalgia rheumatica

VAS: visual analogue scale

Vit: vitamin

↑: increase

↓: decrease

+: positive or in adjunction

+/-: and/or

PRED: prednisone

PTA: Percutaneous transluminal angioplasty

PY: patient-years

QoL: quality of life

RTX: rituximab

SAA: serum amyloid A

s.c.: subcutaneous

subcl: subclavian artery

TA: temporal artery

TAB: temporal artery biopsy

TAK: Takayasu's arteritis

TB: tubercolosis

TCZ: tocilizumab

1. DRUG THERAPY

1.1 THE ROLE OF GLUCOCORTICOIDS

1.1.1 RANDOMISED CONTROLLED TRIALS (GC)

1.1.1.1 Supplementary Table 1. Evidence retrieved for the use of glucocorticoids in giant cell arteritis: overview of included studies

Study ID	Study design	Level of evidence	Intervention overview	Inclusion criteria	Exclusion criteria
GCA					
Glucocorticoids					
Raine et al. 2017 (1)	Feasibility study, prospective, randomised, open-label, blinded evaluator	1b	Efficacy and safety GC modified release (MR) **(Lodotra) vs prednisolone**	Newly diagnosed GCA < 4 weeks, ≥ 50 years, ESR >30 mm/h or CRP > 10 mg/L	GCA on GC treatment > 4 weeks, previous exposure to csDMARD/bDMARD, serious/chronic infections <3 mo, no response to high-GC
Mazlumzadeh et al. 2006 (2)	Double-blind, placebo-controlled, randomised prospective controlled trial	1b	Effect of **high-dose pulse i.v.** methylprednisolone induction therapy to shorten the course of GC treatment	Newly diagnosed GCA, TAB+	GC > 10 mg/day > 10 days prior to enrollment; other chronic inflammatory diseases with acute phase response; active infections; poorly controlled diabetes, angina, congestive heart failure, recent vision loss, amaurosis fugax, TIA.
Cacoub et al. 2001 (3)	Double-blind, randomised prospective controlled trial	1b	Difference in **bone mass loss between prednisone and deflazacort** in newly diagnosed GCA	Newly diagnosed GCA, hospitalized: at least 1: abnormal TA examination; visual abnormalities; jaw pain; compatible headaches + at least one APR (ESR > 40 mm/h, CRP > 3-fold normal value, haptoglobulin,	Bedriedden, GC < 12 mo, uncontrolled infections, pregnancy, creatinine > 120 umol/L peptic ulcer, gout, acute hepatitis, psychotic state, severe hepatic disease, cancer, Paget's, heparine, fluoride, calcitonin, bisphosphonates, hormones < 3 mo, medications leading to hypokalemia, NSAIDs

				orosomucoid or fibrinogen > 2 normal	
Chevalet et al. 2000 (4)	Multicentric, open-label randomised prospective controlled trial	1b	GC-sparing effect of initial **i.v. pulse** of methylprednisolone in simple forms of GCA	Newly diagnosed GCA satisfying ACR criteria or TAB+	Age > 85 years, < 1 mo ocular/vascular involvement (angina, stroke), isolated PMR, visceral defect with life expectancy < 1 year, neoplasia, other inflammatory, hypokalemia

1.1.1.2 Supplementary Table 2. Glucocorticoids: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Raine et al. 2017 (1)	1)No features of active disease and flare-free at 26 weeks. 2)Flare-free in each arm, time to first flare, time to second flare, cumulative GC dose, VAS disease activity, HAQ, QoL (EQ5D, VFQ-25), sleep, fatigue, GC-related toxicity, AE	-Flares: signs/symptoms of active disease: ESR>30mm/h or CRP>10 mg/L + at least 1: (A) sustained fever > 38°C for > 1 week; (B) new, recurrent or worsening headache with scalp or temporal artery pain and tenderness; (C) thickening/ tenderness/ ulcers or nodules over the temporal or occipital arteries; (D) PMR-like symptoms; (E) tongue/jaw claudication; (F) diplopia, blurring of vision, amaurosis fugax; (G) ischemic retinopathy, optic neuropathy, visual loss, transient cerebral ischemia or stroke; (H) absent/weak peripheral pulses suggestive of large vessel vasculitis.	Rheumatologist (clinical assessment and phone calls)	Simple standard analysis	nsp
Mazlumzadeh et al. 2006 (2)	1)Achievement of GC ≤ 5 mg/day at 36 weeks 2)Percentage of pts taking ≤ 5 mg/day at 52 and 78 weeks, median daily dose GC, cumulative GC dose, n of relapses, AE	-Remission: absence of clinical symptoms and normal ESR and CRP values. -Relapse: return of signs or symptoms and/or ↑ ESR or CRP after reduction of GC dose, improved with ↑ GC dose	Same physician for each patient, second physician if doubts on flares	Poisson distribution for relapses	nsp

		-Recurrence: return of signs and/or symptoms and/or changes in lab without GC ≥ 1 mo			
Cacoub et al. 2001 (3)	-Bone mineral density baseline→3,6,12 mo -Vertebral fractures and size variation 12 mo -Calcium/phosphate metabolism baseline→12 mo	-Vertebral fractures: Meunier score (plate collapses, wedging, complete crushes)	DEXA, lab	Chi square and Fisher's exact test	nsp
Chevalet et al. 2000 (4)	1)GC-sparing effect of i.v. pulse methylprednisolone over one-year period 2)Frequency of poor response to GC (corticosteroid resistance and dependence) and complications of GCA and GC AE	-GC sparing: 1) time to 0.3 mg/kg; 2) time to daily dose 7 mg; 3) cumulative doses after 1,2,6,12 mo; 4) daily dose at 12 mo; 5) percentage still on GC after 12 mo -GC resistance: absolute or relative failure of initial treatment to induce remission (disappearance of fever and pain) within a week and/or normalize CRP within 3 weeks -GC dependence: impossibility of proceeding to next dosage level in the reduction scheme without the reappearance of biological and/or clinical symptoms	Physician and inflammation variables	Standard statistics (Wilcoxon rank test, kruskal-wallis test)	nsp

1.1.1.3 Supplementary Table 3. Glucocorticoids: intervention

Study ID	Follow-up duration	Overall n. of patients	Active treatment group	n. of patients	Control group	n. of patients	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Raine et al. 2017 (1)	26 weeks	12	Prednisolone 40-60 mg/day for 4 weeks, then randomised to: 1)standard prednisolone 2)**MR prednisolone**	7	Standard prednisolone taper	5	26-weeks	Reduce by 10 mg/week to reach 40 mg/day by week 4, reduce by 10 mg/2 weeks → 20 mg/day by week 8, reduce by 2-3 mg/2 weeks to reach 10 mg/day by week 16 through 20, reduce by 1 mg/2 weeks to reach 8 mg/day by week 26.	-Return of symptoms/signs of GCA without features of ischemia → previously higher steroid dose. - Symptoms/signs of GCA with jaw/tongue claudication, any or all of A–D with E →40 mg IR prednisolone/MR prednisone daily. - Symptoms/signs of GCA with visual or cerebrovascular disturbance/deficit, any or all of A–E with any or all of F–H → 60 mg prednisolone/MR prednisone/day or IV GC.	nsp
Mazlumzadeh et al. 2006 (2)	52 weeks	27	GC i.v. (methylprednisolone) 15 mg/kg/day for 3 consecutive days + 40 mg/day PRED	14	i.v. saline for 3 consecutive days + 40 mg/day PRED	13	Nsp (52-72 weeks)	Tapered every 2 weeks if controlled disease at 30 mg/day, 25	↑ GC dose by 10 mg if taking ≥ 25 mg/day and by 5	Calcium (1200-1500 mg), vit. D (400-800 IU), bisphosphonates according to

								mg/day, 20 mg/day, 17.5 mg/day, 15 mg/day, 12.5 mg/day, 10 mg/day → then by 1 mg/day/2 weeks	mg if < 25 mg/day or 2 weeks→ taper	densitometry findings
Cacoub et al. 2001 (3)	12 mo	74	Severe GCA: 500 mg methylprednisolone day 1 All: 0.7 mg/kg/day PRED	37	DEFLAZACORT (PRED equivalent dose)	37	Nsp (at least 12 mo)	Initial dose maintained until at least 2 normalised: ESR, CRP, fibrinogen, haptoglobin, orosomucoid → GC taper by 10% until 50% reduction for 1 mo→ by 1 mg/2 weeks→ 10 mg/day	Increase dose of GC	Calcium 1 g/day + calciferol 0.025 mg/day
Chevalet et al. 2000 (4)	12 mo	146	-group 1: 240 mg i.v. methylprednisolone pulse → 0.7 mg/kg/day PRED p.o.	61	-Group 2: NO pulse:0.7 mg/kg/day PRED p.o. -Group 3: 240 mg i.v. pulse → 0.5 mg/kg/day PRED p.o.	Group 2 n=53; group 3 n=50	Nsp (according to clinical practice)	Halve the dose within 1 mo (group 1 and 2 and 20 mg/day within 2 weeks group 3)→ after 6 mo taper to 0 (or 7-12 mg/day if suspension not possible)	Resume of previous GC dose or increased by 5 mg (or 10 mg) for 2 weeks; if no normalization of APR after 3 mo with GC > 20 mg/day → csDMARD If ocular/vascular complications i.v. 500 mg → 1 mg/kg/day	-Nadroparin 6150 international units/day or deltaparin 5000 units) -calcium (1g) and vitamin D2 (8000 IU/week) -Hydrocotrisone (20 mg/day) when PRED ≤ 7 mg/day for adrenal insufficiency for 1 mo after discontinuation → 10 mg/day for 1 mo.

1.1.1.4 Supplementary Table 4. Glucocorticoids: population characteristics and control and comparison

Study ID	Age	% females	GCA subtype	Primary outcome	Results in active treatment group	Results in control group	p-value
Raine et al. 2017 (1)	nsp	nsp	Cranial/LV-GCA/ischaemic (10/12 TAB+)	1)Persistent clinical disease control 2)N flares Cumulative GC Sleep improvement	6/7 1 4067 40.5	4/5 1 3952 58.3	Na Na Na 0.04
Mazlumzadeh et al. 2006 (2)	74 (range 57-89)	19	GCA (TAB+)	-GC ≤ 5 mg/day at week 36 -GC ≤ 5 mg/day at week 52 -GC ≤ 5 mg/day at week 78 -GC cumulative dose week 78 -n relapses	10/14 (71%) 11/14 12/14 5636 21/14	2/13 (15%) 2/13 4/12 7860 37/13	0.003 0.001 0.006 0.001 0.028
Cacoub et al. 2001 (3)	74±1.1 (PRED) vs 70.7±1.3	50	GCA (TAB+ 76% vs 49%)	-Bone mass loss (PRED vs DEFLAZACORT) -Meuniere score vertebral fractures change -Vertebral size variation -Calcium/phosphorus metabolism	-0.026±0.007 g/cm^2 0.77 -0.4 Calcium, phosphorus, vit D, urinary calcium, urinary phosphorus, alkaline phosphates, hydroxyprolinuria	-0.03±0.005 g/cm^2 1.18 -0.2 Calcium, phosphorus, vit D, urinary calcium, urinary phosphorus, alkaline phosphates, hydroxyprolinuria	ns 0.3 0.4 ns
Chevalet et al. 2000 (4)	73.3 (range 56-85)	116	GCA (TAB+ 78%)	-Mean time to reach 0.3 mg/kg (days) -Mean time to 7 mg/day (days) -Mean dose after 12 mo (mg/day) -Mean cumulative dose after 1 mo (mg) -Mean cumulative dose after 2 mo (mg) -Mean cumulative dose after 6 mo (mg) -Mean cumulative dose after 12 mo (mg) -Patients on GC after 12 mo (%)	104.8 255.7 8.37 1084 1811 3973 5777 85	95 and 95.2 254 and 237 7.56 and 8.97 1146 and 848 1916 and 1555 4065 and 3530 5578 and 5168 77 and 89	0.59 0.48 >0.05 >0.05 >0.05 >0.05 0.38 0.31

1.1.1.5 Supplementary Table 5. Glucocorticoids: safety

Study	Type of AE	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for
Raine et al. 2017 (1)	-Serious AE -Diabetes	4	0 2	4 0	nsp	nsp	nsp	nsp	nsp	nsp
Mazlumzadeh et al. 2006 (2)	-AE		38	37	nsp	nsp	nsp	nsp	nsp	nsp
Cacoub et al. 2001 (3)	Not assessed by study	na	na	na	na	na	na	na	na	na
Chevalet et al. 2000 (4)	-AE (infections, cushingoid, rheumatic, psychiatric, CVD, diabetes, digestive, ophthalmologic, phlebitis, myopathy)	111	49	28 and 34	nsp	nsp	nsp	nsp	nsp	nsp

5.2.1.2 Supplementary Table 6. Glucocorticoids: risk of bias assessment (Cochrane bias tool for RCT)

Study	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of participants and personnel (performance bias)**	**Blinding of outcome assessment (detection bias) (patient-reported outcomes)**	**Blinding of outcome assessment (detection bias) (all-cause mortality)**	**Incomplete outcome data (attrition bias) (short-term 2-6 weeks)**	**Incomplete outcome data (attrition bias) (long-term > 6 weeks)**	**Selective reporting (reporting bias)**
Raine et al. 2017 (1)	Low	High	High	High	na	Low	Low	High

Mazlumzadeh et al. 2006 (2)	High	Low	Low	Low	Low	Low	Low	Low
Cacoub et al. 2001 (3)	High	High	Low	Low	na	Low	Low	Low
Chevalet et al. 2000 (4)	High	High	High	High	High	Low	Low	Low

1.1.2 OBSERVATIONAL STUDIES (GC)

1.1.2.1 Supplementary Table 7. Glucocorticoids: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Glucocorticoids						
Prospective						
Hocevar et al. 2016 (5)	Prospective, longitudinal cohort, single centre	2b	Incidence of **permanent visual loss** in GCA with respect to **early diagnosis and GC initiation**, relapse rates and predictors of relapse	Newly diagnosed GCA (ACR criteria + positive TAB or positive CDS) or LV-GCA (ACR criteria + positive PET or positive CDS) followed at least 48 mo	nsp	September 2011-September 2014
Espígol-Frigolé et al. 2013 (6)	Prospective, longitudinal cohort, single centre	4	IL-17 expression on TABs **predicts response to GC** in GCA	GCA TAB+	nsp	1997-2006
Jamilloux et al. 2013 (7)	Prospective, longitudinal cohort, single centre	4	Time to recover of **normal adrenal function** after GC treatment in GCA, predictors of adrenal insufficiency	Consecutive newly diagnosed GCA, satisfying ACR criteria	nsp	1984-2009

Martinez-Taboada et al. 2003 (8)	Prospective, longitudinal cohort, single centre	4	**Homocysteine** levels in GCA and PMR, influence of GC therapy and association with **ischaemic events**	GCA TAB+ or PMR before GC treatment	nsp	nsp
Myklebust et al. 2001 (9)	Prospective population-based cohort, single centre	4	**Prednisolone maintenance dose in relation to starting dose** in PMR and GCA (temporal arteritis)	GCA satisfying ACR criteria TAB+	nsp	1987-1994
Kyle et al. 1989 (10)	Prospective, longitudinal, single centre	4	**High or low steroid regimens in the first 2 mo** of treatment of GCA or PMR	Newly diagnosed, active, untreated GCA or PMR according to Jones and Hazleman criteria	nsp	1982-1985
Retrospective						
Wilson et al. 2017 (11)	Nested case-control analysis on UK Clinical Practice Research Datalink	3b	Nested case-control analysis on UK Clinical Practice Research Datalink (8 million patients) to examine the association of **increasing dose of GC and risk of diabetes, glaucoma, osteoporosis, serious infections, death.**	All pts ≥ 50 years with GCA diagnosis code (ICD-9) with at least one recorded prednisolone prescription at or within 6 mo from GCA diagnosis, and at least 3 years of recorded medical history prior to GCA diagnosis. For each pt at random identification of four control pts without the outcome of interest.	Cancer, HIV, alcoholism, drug abuse	January 1995-august 2013
Restuccia et al. 2017 (12)	Retrospective longitudinal cohort, single centre	4	Retrospective analysis of **long-term (at least 12 mo) remission after discontinuation of GC** in GCA	TAB+ GCA with at least 18 mo fu	nsp	January 1986-December 2007
Broder et al. 2016 (13)	Retrospective medical claims data	4	Retrospective medical claims data to estimate **risks for GC-related AE**	≥2 medical claims with GCA as diagnoses (ICD-9) in the last year and ≥1 oral GC within 6 mo before and after index date	Age<50 years, established GCA	January 2004-December 2009
Chandran et al. 2015 (14)	Retrospective population inception cohort	4	**Comparison of GC dose and duration** between historic cohort (1950-1979) and recent cohort (1980-2009)	Incident GCA cases (ACR criteria) between 1950-2009 identified with Rochester Epidemiology Project (records links)	nsp	1950-2009
Les et al. 2015 (15)	Retrospective cohort	4	**Effectiveness and safety of two GC starting doses**: medium ≤ 30 mg/day vs high > 30 mg/day in newly diagnosed GCA.	Newly diagnosed GCA (ACR criteria): +TAB or clinical (new type of headache, TA abnormalities, new onset jaw	Incomplete data for dates of remission and GC doses or low to fu < 6 mo	January 2004-December 2012

			Predictors of remission with ≤ 7.5 mg/day GC	claudication, ischaemic optic neuropathy + ESR ≥ 50 mm/h or CRP ≥ 2 mg/dl) ≥ 50 years.		
Proven et al. 2003 (16)	Retrospective, population-based	4	**Course of GC therapy and related AE** in newly diagnosed GCA	All newly diagnosed GCA (ACR criteria) included in the Rochester Epidemiology Project	GC > 1 week prior to GCA diagnosis	1950-1991
Hernández-rodríguez et al. 2002 (17)	Retrospective, single centre	4	**Strong initial systemic inflammation** (circulating pro-inflammatory cytokines) is associated with **higher and longer GC requirements**	GCA TAB+	Transferred to other institution, low compliance, dies < 3 mo from diagnosis	14 years
Delecoeuillerie et al. 1988 (18)	Retrospective, single centre	4	Effect on outcome of **different initial GC doses according to clinical manifestations**	Newly diagnoses GCA or PMR (four of the following required: 1) recent temporal or occipital pain or scalp tenderness; 2) jaw claudication; 3) tender, swollen TA, thickening or reduced pulse; 4) transient or sudden visual loss, ophthalmoplegia or blurred vision; 5) general symptoms; 6) age > 50; 7) ESR > 30/h, increase orosomucoid and haptoglobin.	nsp	1976-1986

1.1.2.2 Supplementary Table 8. Glucocorticoids: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Hocevar et al. 2016 (5)	Rate of permanent visual loss, relapse rate and predictors with respect to early diagnosis and GC treatment	-Early GCA: diagnosed and treated within 30 days of symptoms onset -Late GCA: > 30 days -Permanent visual loss: new onset of permanent reduction of visual acuity or visual field loss. -Relapse: disease worsening or new disease activity during GC taper after remission.	2 rheumatologists.	Standard statistics, Kaplan-Meier for time to first relapse	nsp

Espígol-Frigolé et al. 2013 (6)	IL-17A expression in TAB lesions and its relationship with disease outcome	-Relapse: reappearance of cranial symptoms, PMR r systemic symptoms that resolved by increase GC of 10 mg above previous effective dose	Rheumatologist, real-time PCR for IL-17 mRNA, immunohistochemistry	Mann-whitney, Spearman's, Kaplan-meier	nsp
Jamilloux et al. 2013 (7)	Adrenal function	ACTH stimulation test. Cortisol concentration ≥ 580 nmol/L normal response; < 580 nmol/L non reponsers	Rheumatologist, ACTH test annually until recovery in non-responders	Comprehensive questionnaire	nsp
Martinez-Taboada et al. 2003 (8)	Homocysteine levels compared to healthy controls, influence of GC on homocysteine levels, association with ischaemic complications	-Remission: absence of clinical symptoms and signs of disease + normal lab values	Physician	Wilcoxon rank-sum test	nsp
Myklebust et al. 2001 (9)	Estimate maintenance dose of GC and rate of GC cessation during first 2 years of treatment	-Maintenance GC dose: lowest effective and stable dose providing relief of symptoms during first and second year of treatment	Rheumatologist	Chi squared Mann-whitney	Pts who discontinued GC due to reasons other than remission
Kyle et al. 1989 (10)	High vs low GC regimens first 2 mo	-Disease activity: 1) Active disease: no improvement from previous visit or relapse; 2) Symptoms/signs of activity still present but definite improvement from previous visit; 3) well, symptoms/signs resolved	Physician	Chi squared	nsp
Wilson et al. 2017 (11)	Frequency of incident diabetes, glaucoma, osteoporosis, bone fracture, serious infection, death	-GC cumulative dose: if no information on prescription quantity, the most frequently used prescription quantity in GCA cohort was used. For missing values, a default value of 1 tablet per day.	Database records	Conditional logistic regression, stepwise regression analysis	Pts followed up to an outcome of interest, death, left database or study period ended

		-Past GC use: > 365 days prior to index date -Recent use: 180-365 days prior to index date -Current use: < 180 days prior to index date.			
Restuccia et al. 2017 (12)	Frequency and predictors of long-term remission after discontinuation GC	-Long-term remission: permanent discontinuation of PRED without recurrence of symptoms and elevation of APR for at least 1 year.	Clinical records	Cox proportional hazard ratios for predictors of remission	nsp
Broder et al. 2016 (13)	Presence of a new GC-related AE during the post-index period	-Index date: first date of GCA diagnosis -Bone AE: fractures, OP, aseptic necrosis of bone, hip-replacement -Cumulative GC exposure: from 1 year before index date and daily dose thereafter. -N of chronic conditions calculated with Healthcare Cost and Utilization Project Chronic Condition Indicator and Charlson comorbidity index	Database records (Truven Health Analytics MarketScan Database: health insurance claims)	Cox regression with GC use as a time-dependent variable	Pts without any AE were censored at the end of follow-up. For individual AE analyses, patients without that AE were censored at the end of follow-up.
Chandran et al. 2015 (14)	Cumulative GC dose and duration: differences between historic and recent cohort	-GC discontinuation: physician instructions for discontinuation and no record of any GC use thereafter for at least 6 mo	Medical records and prescription information	Historic cohort (1950-1979) and recent cohort (1980-2009)	All records followed until death, migration or December 31 2009
Les et al. 2015 (15)	1)Remission with PRED ≤ 7.5 mg/day 2)Time to GC withdrawal, cumulative GC dose at 6 and 12 mo, relapses, GC-	-Clinical remission: complete absence of signs/symptoms GCA for at least 1 week -Biological remission: normalisation of ESR and CRP in two consecutive measurements at least 1 week apart.	Rheumatologist	Cox regression	nsp

	related AE, GCA-related complications, death	-Relapse: reappearance of signs/symptoms of GCA +/- ↑ APR that required ↑ GC dose or MTX dose.			
Proven et al. 2003 (16)	GC course and GC-related AE in newly diagnosed GCA	nsp	Physician	Cox proportional hazard models	nsp
Hernández-rodríguez et al. 2002 (17)	Inflammatory response to predict GC response	-Flare: ESR >50 mm/h + GCA manifestations or Hb < 110 g/L/ worsening symptoms + normal or slightly ↑ ESR + resolution of symptoms after GC ↑ -Systemic inflammatory response: fever, weight loss, ESR ≥ 85 mm/h, Hb < 110 g/L: weak if ≤ 2; strong ≥ 3	Physician ELISA for IL1ß, TNF, IL6	Standard statistics, Kaplan Meyer for time to GC < 10 mg/day	nsp
Delecoeuillerie et al. 1988 (18)	Whether high doses of GC are useful to treat GCA or PMR and influence the course of disease	-Remission: prolonged absence of symptoms, allowing withdrawal of GC -Relapse: recurrence of clinical symptoms after treatment withdrawal requiring its reinstitution	Rheumatologist	Standard statistics (Chi squared)	nsp

1.1.2.3 Supplementary Table 9. Glucocorticoids: intervention/treatment characteristics

Study ID	Follow-up duration	Patient-years	Overall n. of patients	Intervention	Control	Treatment group	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Hocevar et al. 2016 (5)	48 mo (median 104 weeks (IQR 53-126)	nsp	73→68 included (early GCA: n=39), late GCA (n=29)	GC → csDMARD (LEF or MTX)	na	-Uncomplicated disease: GC (methylprednisolone) p.o. 32-48 mg/day -Ischaemic (44%): GC	At least 1.5 years maintenance GC dose	GC taper after 2-4 weeks by 4 mg/week to 16 mg/day→ taper 2 mg/week to 8 mg/day for 1 mo→taper 1	GC ↑ by 8-12 mg over last dose + LEF 20 mg/day or MTX 15 mg/week	ASA all patients

						(methylprednisolone) i.v. 250 mg/day on 3 consecutive days		mg/mo to 4 mg/day for 1.5 years		
Espígol-Frigolé et al. 2013 (6)	4.5 years (52-464 weeks)	nsp	57 (full analysis on 38 treatment naïve)	Treatment naïve (n=38)→ GC (PRED) 60 mg/day for median 7 days	19	Standard care GC	nsp	nsp	Increase by 10 mg above last effective dose	nsp
Jamilloux et al. 2013 (7)	nsp	nsp	150	GC + ACTH test at GC dose < 5 mg/day	na	-no ischaemic symptoms: GC (PRED) 0.7 mg/kg/day until symptoms free and CRP < 5 mg/L -ischaemic symptoms: 1 mg/kg/day, often preceded by pulse methylprednisolone	nsp	Taper 0.35 mg/kg/day within 4—6 weeks, then taper by 10 mg/day every 2 weeks → 30 mg/day, then by 5 mg/day every 2-3 weeks → 20 mg/day then by 2.5 mg/day every 15-21 days → 10 mg/day then by 1 mg/day every month until 5 mg/day.	nsp	Hormone substitution if negative response to ACTH test
Martinez-Taboada et al. 2003 (8)	nsp	nsp	-17 GCA -39 PMR -23 healthy controls	GCA: GC 40-60 mg (15-20 3 times per day)	na	GC 40-60 mg (15-20 3 times per day)	nsp	According to clinical disease activity	nsp	nsp
Myklebust et al. 2001 (9)	Nsp (2 years)	nsp	-37 GCA -19 GCA+PMR -217 PMR	Initial GC→ maintenance GC	na	-GCA: 48.8 mg/day (5-120 mg) -GCA/PMR:32.6 mg/day (10-80 mg)	nsp	Nsp, not fixed scheme	nsp	nsp
Kyle et al. 1989 (10)	2 mo	nsp	36 GCA: 15 low GC dose; 20 high-dose 39 PMR	GCA (n=20): GC HIGH DOSE (40 mg/day/5 days→ 40	GCA (n=15): GC LOW DOSE	GCA High or low GC regimen first 2 mo	2 mo	nsp	Increase in GC dose	nsp

				mg/day/4 weeks→30 mg/day/2 weeks→20 mg/day/2 weeks	(40 mg/day /5 days→ 20 mg/day /4 weeks →15 mg/day /2 weeks →10 mg/day /2 weeks					
Wilson et al. 2017 (11)	nsp	nsp	5011	321 diabetes	1272 matched controls	GC high vs low dose	Highest GC dose (30 mg/day) 43–74 days (cases) 20–50 days (controls)	nsp	nsp	nsp
				243 glaucoma	1821 matched controls					
				408 fractures	1586					
				511 OP	1821					
				408 fractures	1586					
				433 serious infection	1421					
				517 death	1774					
Restuccia et al. 2017 (12)	84 (IQR 54-127)	nsp	131	Standard care GC	na	GC mean PRED 47 ± 15 mg/day, some with visual ischemic	na	PRED initial dose for 1 mo→ tapered by 5 mg/2-4 weeks to	nsp	nsp

						methylprednisolone (1g/day for 3 consecutive days) followed by PRED 60 mg/day + MTX (n=4)		20 mg/day → BY 2.5 MG/2-4 weeks to 10 mg/day → 1 mg/1-2 mo until suspension		
Broder et al. 2016 (13)	Mean 3.9 years/patients	9680	2947	Standard care GC+/- csDMARD or bDMARDs	na	GC cumulative dose 6983.3 mg ± 6519.9	1196±792.2	nsp	nsp	nsp
Chandran et al. 2015 (14)	9.5 years	nsp	205	GC 60 mg/day then tapered	na	GC 60 mg/day then tapered +/- csDMARD (MTX n=8; Cyc n=2; AZA n=5)	Mean 2.6 years vs 1.5 years	nsp	nsp	nsp
Les et al. 2015 (15)	Median 2.85 (95%CI 2.57-3.52)	nsp	103 -Medium dose: 53 -High dose: 50	GC medium dose (≤ 30 mg/day) +/- methylprednisolone pulses (250-500 mg for 3 days: 32%) and/or MTX (7.5-20 mg/week: 49%)	GC high dose (> 30 mg/day) +/- methylprednisolone pulses (16%) and/or MTX (32%)	GC (comparison of different doses): Medium dose: 27.45±5.51 m/day; High dose: 54.30±11.86	nsp	No protocol, adjusted by physician on basis of clinical and lab parameters	Increase GC dose by 5-10 mg/day	ASA, calcium+vit D, bisphosphonate if indicated Cardiovascular assessment (periodic blood pressure, diabetes, hypercholesterolemia)
Proven et al. 2003 (16)	10 years (range 0.1-34 years)	nsp	120	Standard care GC	na	Median GC 60 mg/day PRED (range 10-100 mg/day)	21.6 (range 2.3-122) mo	nsp	nsp	nsp
Hernández-rodríguez et al. 2002 (17)	nsp	nsp	75	Standard care GC	na	GC 1 mg/kg/day (up to 60 mg/day) for 1 mo	nsp	GC tapered by 5 mg/week → 20 mg/day→ slower taper	GC ↑ to 10 mg above previous efficacious dose	nsp

Delecoeuillerie et al. 1988 (18)	30.9 mo	nsp	210 (GCA n=78)	GC different doses	na	-Visual symptoms: 1 mg/kg/day -High dose (group B=GCA); 1) 10-20 mg/day (n=25); 2) 21-59 mg/day (n=28); 3) 60-90 mg/day (n=25)	Group B: 30.9±14	Adjusted to minimal dose sufficient to control symptoms and keep ESR < 30 mm/h	Increased if initial dose ineffective	nsp

1.1.2.4 Supplementary Table 10. Glucocorticoids: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Disease duration at treatment start	Primary outcome	Results in active treatment group	Results in control group	p-value
Hocevar et al. 2016 (5)	73.2 (IQR 67.3-76.1)	72%	GCA (TAB+ 82%; CDS+ 78%); LV-GCA (CDS+ in 36%, PET+ 100%)	Median 30 days (≤ 30 days in 57% of patients)	-Relapse rate (early vs late GCA)	Overall 46% 17/39 (early) vs 14/29 (late)	na	0.807
					-Time to first relapse	24.8 weeks (IQR 13.6-46.5) at GC dose 6 mg (IQR 4-12)	na	na
					-Predictors of relapse	Higher ESR and CRP, SAA, haptoglobin, fibrinogen, white blood cell count at baseline	na	na
Espígol-Frigolé et al. 2013 (6)	78	45	GCA TAB+	nsp	-IL17-A mRNA concentrations in TAB (sustained remission vs relapsers)	7.46±9.73 vs 3.19±3.70	na	0.058
					-IL17-A mRNA (GC discontinuation vs non discontinuation at 3 years)	5.17±8.11 vs 0.29±0.46	na	0.06
Jamilloux et al. 2013 (7)	74±7	101 (67%)	GCA (71% TAB+)	17.1 mo (range 5-71 mo)	-ACTH test non-responders (adrenal insufficiency)	74 (49%); mean time until recovery of adrenal function 14 mo	na	na
					-predictors of adrenal insufficiency	-GC > 15 mg/day at 6 mo, > 9.5 mg/day at 12 mo, treatment duration > 19 mo, cumulative GC dose > 8.5 g, basal cortisol < 386 nmol/L	na	<0.005

Martinez-Taboada et al. 2003 (8)	73±5.6	76%	GCA TAB+	nsp	-Homocysteine levels (GCA vs healthy controls)	higher		<0.05
					-Homocysteine levels GCA (pre and post-GC)	13.4±3.3 → 17.8±5 umol/L	na	0.003
					Homocysteine levels GCA (ischaemic vs non-ischaemic)	15±4.9 vs 11.6 ±1.9	na	0.1
Myklebust et al. 2001 (9)	70 (GCA) 76 (GCA+PMR)	nsp	GCA TAB+ GCA/PMR PMr	1.4 mo (GCA) 1.6 mo (GCA+PMR)	-Minimal maintenance dose during 1st year	6.6 mg/day (GCA) 8.3 mg/day (GCA+PMR)	na	na
					-Minimal maintenance dose during 2nd year	4.1 mg/day (GCA) 4.7 mg/day (GCA+PMR)	na	na
					-GC discontinuation after 1st year	5% (GCA) 0 (GCA+PMR)	na	na
					-GC discontinuation after 2nd year	16% (GCA) 5% (GCA+PMR)	na	na
Kyle et al. 1989 (10)	nsp	nsp	GCA or PMR	nsp	-Relapses (high vs low GC dose)	4/20 (20%) vs 6/15 (40%)	na	na
Wilson et al. 2017 (11)	Details on 5 age groups	76.9% vs 77.6%	GCA	nsp	GC-related AE	na	na	na
	Details on 5 age groups	88.8% vs 87.6%	GCA	nsp	GC-related AE	na	na	na
	Details on 5 age groups	76.5% vs 76.6%	GCA	nsp	GC-related AE	na	na	na
	Details on 5 age groups	76.5% vs 76.6%	GCA	nsp	GC-related AE	na	na	na
	Details on 5 age groups	nsp	GCA	nsp	GC-related AE	na	na	na
	Details on 5 age groups	nsp	GCA	nsp	GC-related AE	na	na	na
Restuccia et al. 2017 (12)	74± 7	103 (79%)	GCA (TAB+)	nsp	-Long term remission frequency	73 (56%)	na	na
					-N of flares (long-term remission vs not)	21/73 (28.8%) vs 32/58 (55.2%)	na	0.002
					-Cumulative GC dose (long-term remission vs not)	8.7±5 vs 17.9±11.7	na	<0.0001

					-Duration of therapy (long-term remission vs not)	20 (IQR 13,33) vs 59 (28,96)	na	<0.0001
					-Predictors of remission	PMR: HR 0.46 (95%CI 0.26-0.82)	na	0.008
						Aneamia: HR 1.48 (95%CI 1.18-1.84	na	<0.0001
Broder et al. 2016 (13)	71±10.6	71%	GCA	nsp	GC-related AE	na	na	na
Chandran et al. 2015 (14)	76.2±8.3	79%	GCA TAB+	nsp	-GC cumulative dose (recent vs historic)	6.3 g vs 4.1 g (1 year) 10.7 vs 7.6 g (5 years)	na	<0.001
					-Time to GC discontinuation (recent vs historic)	2.6 years vs 1.5 years	na	<0.001
Les et al. 2015 (15)	74.7±8.4 (medium) vs 73.3±7.9 (high)	70% vs 62%	GCA (52% TAB+)	nsp	-Remission with PRED ≤ 7.5 mg/day	100%	96%	0.14
					-Time to remission (medium vs high GC)	186 days (147-233)	236 days (177-276)	HR: 1.70 (1.12-2.57); p=0.01
					-Cumulative PRED dose at 6 mo	2.47±0.7 g	3.86±1.85 g	<0.001
					-Associated factors with remission	Methylprednisolone pulses		HR 2.21 (1.31-3.71); p=0.003
Proven et al. 2003 (16)	75 (range 56-92)	100 (83%)	GCA	nsp	-Time to reach GC ≤ 7.5 mg/day	Median 6.5 mo	na	na
					-Time to reach GC ≤ 5 mg/day	Median 7.5 mo	na	na
					-GC discontinued	87 (after median 22 mo)	na	na
Hernández-rodríguez et al. 2002 (17)	76 (weak inflammation) vs 73 (strong)	49 -40 weak inflammatory response -35 strong response	GCA TAB+	14 (weak inflammation) vs 16 (strong)	-Time to GC < 10 mg/day (weak vs strong inflammatory response)	Median 40 weeks (95%CI 37-43) in 50% of patients vs 62 (95%CI 42-82)	na	0.0062
					-cumulative GC dose	8974±3939 g vs 6893±3075 g	na	0.01

					-N of flares	22 (55%) vs 35 (77%)	na	0.054
Delecoeuillerie et al. 1988 (18)	75.4±7.1 (pure GCA)	30	GCA (TAB+ n=60)	nsp	-Remission (10-20 mg vs 21-59 vs 60-90)	Mean 14.56 vs 15.54 vs 11.44	na	ns
					-Relapse (10-20 mg vs 21-59 vs 60-90)	8.32 vs 8.29 vs 5.20	na	ns

1.1.2.5 Supplementary Table 11. Glucocorticoids: safety/events

Study ID	Type of AE	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for	p-value/Predictors/associated factors
Hocevar et al. 2016 (5)	-Permanent visual loss	5.9%	na	na		RR (GCA vs LV-GCA)	5.7	na	na	nsp	0.102
						RR (late vs early GCA)	4	na	na	nsp	0.177
Espígol-Frigolé et al. 2013 (6)	Not assessed by study	na	na	na	na	na	na	na	na	na	na
Jamilloux et al. 2013 (7)	-AE	90%	na	na	na	na	na	na	na	na	na
	-AE (GC-related)	103 (86%)	na	na	na	na	na	na	na	na	Median time from GC to AE 1.1 years (mean 2.7 years). Higher initial GC dose and higher cumulative

											dose were risk factors
Martinez-Taboada et al. 2003 (8)	Not assessed by study	na	na	na	na	na	na	na	na	na	na
Myklebust et al. 2001 (9)	Not assessed by study	na	na	na	na	na	na	na	na	na	na
Kyle et al. 1989 (10)	Not assessed by study	na	na	na	na	na	na	na	na	na	na
Wilson et al. 2017 (11)	-Diabetes (GCA in highest daily dose prednisolone (30 mg/day) vs lower daily dose (5 mg/day)	na	na	na	na	OR	na	na	4.7 (95% CI: 2.8–7.8),	Multivariate analysis based on significant results	na
	-OP	na	na	na	na	OR	na	na	1.9 (95% CI: 1.2-2.9)	Multivariate analysis based on significant results	na
	-Fractures	na	na	na	na	OR	na	na	2.6 (95% CI:1.6-4.3)	Multivariate analysis based on significant results	na
	-Glaucoma	na	na	na	na	OR	na	na	3.5 (95%CI 2.0-6.1)	Multivariate analysis based on significant results	na
	-Serious infections	na	na	na	na	OR	na	na	3.3 (95%CI 2.2-5.2)	Multivariate analysis based on significant results	na
	-Death	na	na	na	na	OR	na	na	2.1 (95%CI 1.3-3.5)	Multivariate analysis based on significant results	na

Restuccia et al. 2017 (12)	Not assessed by study	na	na	na	na	na	na	na	na	na	na
Broder et al. 2016 (13)	AE rate	0.43/PY	na	na	na	HR	na	na	1.03; 95%CI 1.02-1.05	Each 1000-mg increase in GC exposure, adj for age, sex, geographic region, n chronic conditions, Charlson comorbidity index, diabetes	p<0.001
	-Bone AE	0.156/PY	na	na	na	HR	na	na			<0.001
	-Cataract	0.158/PY	na	na	na	HR	na	na			<0.001
	-Glaucoma	0.022/PY	na	na	na	HR	na	na			0.005
	-Pneumonia	0.068/PY	na	na	na	HR	na	na			0.003
	-Opportunistic infections	0.010/PY	na	na	na	HR	na	na			<0.001
Chandran et al. 2015 (14)	-GC-related AE (recent vs historic cohort) by 10 years after diagnosis	57% vs 50%	na	na	na	na	na	na	na	na	0.52
	-Wrist fracture	9	na	na	na	HR (recent vs historic)	2.59 (95% CI: 0.32-20.81)	na	na	na	Na
	-GI bleeding	19	na	na	na	HR	3.2 (95%CI: 0.73-14.10)	na	na	na	na

	-Infections	93	na	na	na	HR	1.58 (95%CI 0.93-2.67)	na	na	na	na
Les et al. 2015 (15)	-AE	nsp	23 (43%)	33 (66%)	na	na	na	na	na	na	0.02
	-Diabetes	nsp	6 (11%)	10 (20%)	na	na	na	na	na	na	0.02
	-Hypertension	nsp	2 (3%)	2 (4%)	na	na	na	na	na	na	0.95
	-Hypercholesterolemia	nsp	5 (9%)	15 (30%	na	na	na	na	na	na	0.008
	-Fractures	nsp	5 (9%)	7 (14%)	na	na	na	na	na	na	0.47
	-Cataract	nsp	4 (7%)	5 (10%)	na	na	na	na	na	na	0.74
	-Serious infections	nsp	6 (11%)	3 (6%)	na	na	na	na	na	na	0.49
	-Cushingoid	nsp	1 (2%)	4 (8%)	na	na	na	na	na	na	0.19
	-GCA-Ischaemic ocular	nsp	0	0	na	na	na	na	na	na	1.00
	-GCA-stroke	nsp	1 (2%)	1 (2%)	na	na	na	na	na	na	0.97
	-Aneurysm	nsp	1 (2%)	3 (6%)	na	na	na	na	na	na	0.35
Proven et al. 2003 (16)	-AE	103 (86%)	na	na	na	na	na	na	na	na	Associate with age and cumulative GC dose. Median time to first AE 1.1 years (mean 2.7 years)
	-Diabetes	9 (11%)	na	na	na	na	na	na	na	na	na
	-Fractures	46 (38%)	na	na	na	na	na	na	na	na	na
	-GI bleeding	5 (4%)	na	na	na	na	na	na	na	na	na
	-Hypertension	26 (22%)	na	na	na	na	na	na	na	na	na
	-Infections	37 (31%)	na	na	na	na	na	na	na	na	na
	-Cataract	29 (41%)	na	na	na	na	na	na	na	na	na
	-Death	23 (19%) (3 GCA-related)	na	na	na	na	na	na	na	na	na

Hernández-rodríguez et al. 2002 (17)	Not assessed by study	na	na	na	na	na	na	na	na	na	na
Delecoeuilleri e et al. 1988 (18)	AE (GC-related) (10-20 mg vs 21-59 vs 60-90)	3.12 vs 16.57 vs 22.88	na	na	na	na	na	na	na	na	<0.001
	Visual/neurologic complications (10-20 mg vs 21-59 vs 60-90)	1.4 vs 1.4 vs 4.16	na	na	na	na	na	na	na	na	Ns (more frequent in male than female)

1.1.2.6 Supplementary Table 12. Glucocorticoids: risk of bias assessment (Newcastle-Ottawa scale for cohort studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two ∗)
Hocevar et al. 2016 (5)	∗	∗	∗	∗	na	Self-report	∗	∗	6
Espígol-Frigolé et al. 2013 (6)	∗	na	no	∗	na	Self-report	∗	∗	4
Jamilloux et al. 2013 (7)	∗	na	∗	∗	na	Self-report	∗	nsp	4
Martinez-Taboada et al. 2003 (8)	∗	∗	∗	∗	nsp	Self-report	nsp	nsp	4
Myklebust et al. 2001 (9)	∗	na	nsp	∗	na	Self-report	∗	∗	4

Kyle et al. 1989 (10)	*	*	nsp	*	no	Self-report	nsp	nsp	3
Restuccia et al. 2017 (12)	*	na	no	*	na	Self-report	*	nsp	3
Broder et al. 2016 (13)	*	na	*	*	na	*	*	*	6
Chandran et al. 2015 (14)	*	na	*	*	na	*	*	nsp	5
Les et al. 2015 (15)	*	*	no	*	*	Self-report	*	nsp	5
Proven et al. 2003 (16)	*	na	*	*	na	*	*	*	6
Hernández-rodríguez et al. 2002 (17)	*	na	nsp	*	na	Self-report	nsp	*	3
Delecoeuillerie et al. 1988 (18)	*	*	no	*	nsp	Self-report	*	*	5

1.1.2.7 Supplementary Table 13. Glucocorticoids: risk of bias assessment (Newcastle-Ottawa scale for case-control studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Exposure** 1)Ascertainment of exposure	**Total n of stars** (only comparability can have two *)
Wilson et al. 2017 (11)	*	*	*	*	**	*	7

1.2 THE ROLE OF METHOTREXATE AND OTHER NON-BIOLOGIC IMMUNOSUPPRESSIVE DRUGS

1.2.1 RANDOMISED CONTROLLED TRIALS (MTX/other csDMARDs)

1.2.1.1 Supplementary Table 14. Evidence retrieved for the use of methotrexate and othe non-biologic immunosuppressive druges: overview of included studies

Study ID	Study design	Level of evidence	Intervention overview	Inclusion criteria	Exclusion criteria
GCA					
METHOTREXATE					
Hoffman et al. 2002(19)	Multicenter, randomised, double-blind, placebo-controlled trial	1b	GC + **MTX** *vs* GC + placebo	**Newly diagnosed GCA** for < 6 months (cranial, LV-GCA or ischaemic).	Previous dx of PMR/GCA, relapsed GCA, previous GC treatment > 21 days. No improvement after 5 days of tx.
Jover et al. 2001 (20)	Randomised, double-blind, placebo-controlled trial	1b	GC + **MTX** *vs* GC + placebo	**Newly diagnosed TAB+ active GCA**, < 2 weeks GC	Low GC treatment > 3 months, other immunosuppressive, contraindications to MTX, neoplasm < 5 years
Spiera et al. 2001 (21)	Randomised, double-blind, placebo-controlled trial	1b	GC + **MTX** *vs* GC + placebo	**Newly diagnosed GCA < 1 mo** (+ and neg TAB + clinical features including LV-GCA or ischaemic)	Immunosuppressive drugs < 1-year, Active infection, neoplasia, connective tissue disease, contraindications to MTX
Van der Veen et al. 1996 (22)	Randomised, double-blind placebo-controlled trial	1b	GC + **MTX** *vs.* GC + placebo	**Newly diagnosed, active, untreated PMR or GCA or both**	Active infections, other connective tissue disease, liver pathology contraindicating MTX
CYCLOSPORINE					
Schaufelberger et al. 1998 (23)	Open-label, randomised controlled trial	1b	GC + CsA vs GC	**Refractory GCA** according to Bengtsson and Malmvall criteria for ≥ 1 year and > 5 mg PRED/day	nsp

Schaufelberger et al. 2006 (24)	Open-label, multicentre, randomised controlled trial	1b	GC + CsA vs GC	**Consecutive GCA patients** according to ACR, TAB+	Signs of threatening vascular ischaemia, infection, previous malignancy, uncontrolled hypertension, reduced renal function, w1 month's duration of GC treatment and ongoing combination with any other immunomodulator.
DAPSONE					
Liozon et al. 1993 (25)	Open-label, randomised controlled trial	1b	GC + dapsone vs GC	**GCA** TAB+	nsp
GCA + PMR					
AZATHIOPRINE					
De Silva et al. 1986 (26)	Randomised, double-blind, placebo-controlled trial	1b	GC (low dose) + AZA vs GC + placebo	**Established GCA or PMR or both** according to Jones and Hazleman criteria with disease duration > 1 year and maintenance GC dose > 5 mg/day	nsp

1.2.1.2 Supplementary Table 15. Methotrexate and other csDMARDs: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Hoffman et al. 2002 (19)	1)First disease relapse and treatment failure. 2) clinical features associated with relapse, disease-related morbidity, total dose and duration of GC treatment, treatment-associated toxicities, death.	-Relapse: change in ESR from normal to 40 mm/hour + at least 1 other feature of GCA. - Treatment failure: 2 disease relapses/a relapse not responsive to GC dose increase	2 Rheumatologist (clinically)	-Intention-to-treat -Kaplan-Meyer -log-rank test -cox-proportional hazards model	Stop experimental drug after treatment failure.

Jover et al. 2001 (20)	Number of relapses and total cumulative dose of prednisone during follow-up.	Relapse: recurrence of GCA symptoms after definite objective improvement followed by symptom reversal on resumption of or increases in the prednisone dose.	3 rheumatologists (clinically)	-completion of follow-up and completion of treatment	nsp
Spiera et al. 2001 (21)	1)Cumulative GC dose. 2) Total duration of GC treatment, length of time to reach a 10 mg/day, numbers of flares.	Relapse: recurrence of prior or the development of new GCA symptoms after objective improvement, and reverse upon resumption or increase in GC dose.	Rheumatologist (clinically), study and treating physician	-standard methods	nsp
Van der Veen et al. 1996 (22)	nsp	-Remission: defined at time of discontinuing GC and MTX -Relapse: recurrence of original symptoms + increase of 100% in ERS/CRP while on GC -Recurrence: recurrence of original symptoms + increase of 100% in ESR/CRP after stop GC and MTX	nsp	-standard methods	nsp
Schaufelberger et al. 1998 (23)	Nsp (Efficacy and safety of Cyclosporine to treat refractory GCA)	nsp	nsp	nsp	nsp
Schaufelberger et al. 2006 (24)	1)Maintenance and total accumulated GC dosages at study end 2)Number of flares and number	nsp	nsp	nsp	nsp

	of patients in complete remission				
Liozon et al. 1993 (25)	Steroid-sparing effect of Dapsone	Clinical and acute phase reactants normalisation	nsp	nsp	nsp
De Silva et al. 1986 (26)	Steroid-sparing effect of AZA on maintenance GC dose	na	Rheumatologist	Standard methods	nsp

1.2.1.3 Supplementary Table 16. Methotrexate and other csDMARDs: intervention

Study ID	Follow-up duration	Overall n. of patients	Active treatment group	n. of patients	Control group	n. of patients	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Hoffman et al. 2002 (19)	4 years	98	- **PRED** 1 mg/kg/day (<60 mg/day) + -0.15 mg/kg/week **MTX** (in-creased to 0.25 mg/kg/week, for a maximum dosage of 15, p.o.	51	placebo	48	-MTX: 12 months -GC: 6 months	- GC: after 4 weeks, reduced by 5 mg every 4 days on alternate-day schedule → 60 mg every other day after 3 months, then reduced by 5 mg/week until discontinuation. -MTX: 2.5 mg/month until discontinuation	Previous effective dose of GC plus additional 10 mg. Taper after 1 month.	-folinic acid 5 mg/week -Calcium 1000 mg+vit D 0.25 ug twice/week -bone protection left to physician
Jover et al. 2001 (20)	24 months	42	**PRED** 60 mg/d (3 divided doses first week, then once daily) + **MTX** 10 mg/week, p.o.	21	placebo	21	-MTX: 24 months	-GC: Tapered by 10 mg/week until 40 mg/d by end of first month. Then, taper by 5 mg/week → 20 mg/d end of second month. Then taper by 2.5 mg/2 weeks until stopped. Faster or slower tapering allowed	Dose of PRED increased to the minimum amount that controlled symptoms, MTX increased by	-Folic acid 5 mg/day -Calcium 1000+vit D 600 -Isoniazide prophylaxis if history/signs of TB

									2.5 mg per week.	
Spiera et al. 2001 (21)	nsp	21	PRED oral 1 mg/ kg/day suggested (40-1000 mg according to treating physician, 3 treated with i.v. pulses) + **MTX** 7.5 mg p.o. when GC dose of 30 mg/day	12	placebo	9	nsp (duration of GC treatment 68 weeks in I, 60 in C)	-GC: tapered by 10 mg/week to 40 mg/day once clinical/lab abnormalities revolved, then by 5 mg/week to 20 mg by the end of the second month then by 2.5 m g/week until withdrawal. -MTX: after GC withdrawal, tapered by 2.5 mg/week per month to stop.	Dose of GC increased by treating physician.	-Folic acid 1 mg/day -Calcium 1500 mg, vit D 800 IU. -bone protection left to physician
Van der Veen et al. (22)	24 months (at least 12 months after discontinuing medications)	40	PRED 20 mg/day + MTX 7.5 mg p.o.	20 (3 with GCA)	placebo	20 (3 with GCA)	-GC: median 47.5 (3-104) -MTX: after GC discontinuation	-GC: tapered by 2.5 mg/3 weeks as soon as symptoms resolution and normalization or ESR/CRP → 7.5 mg/day then taper by 2.5 mg/6 weeks. -MTX: after GC withdrawal, once every two weeks for 3 administrations then stop.	GC dose doubled (to max 20 mg/daily) until symptoms revolved and ESR/CRP normalised	-calcium
Schaufelberger et al. 1998 (23)	6 mo	22 (21 complete)	PRED (mean 11.8±10 mg/day) + CsA (2 mg/kg/day)	11	GC (mean 11.1±7 mg/day)	11	nsp	nsp	nsp	nsp

Schaufelberger et al. 2006 (24)	12 mo	59	PRED (mean 40±11 mg/day) + CsA (2-3.5 mg/kg/day)	29	PRED (mean 40±12 mg/day)	30	12 mo	GC were tapered according to individualised protocol; CsA reduced according to renal function and hypertension	nsp	nsp
Liozon et al. 1993 (25)	nsp (continued for 3 mo after stopping GC)	47	PRED (0.7 mg/kg/day-1 mg/kg/day if ocular) + Dapsone	24	PRED (0.7 mg/kg/day-1 mg/kg/day if ocular)	23	14 mo + 3 mo vs 13 mo + 3 mo	After good clinical control PRED tapered to 50% over 4 weeks until withdrawal	nsp	nsp
De Silva et al. 1986 (26)	52 weeks	31 (complete data at end fu only in 21)	Prednisolone maintenance dose (8.1 vs 7.4 mg/day) + AZA (100-150 mg/day) p.o.	16 (complete data on 9)	placebo	15 (complete data 12)	Prednisolone maintenance dose (8.1 vs 7.4 mg/day) + AZA (100-150 mg/day) p.o.	Nsp, AZA not tapered	nsp	metoclopramide 5 mg if nausea

1.2.1.4 Supplementary Table 17. Methotrexate and other csDMARDs: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Primary outcome	Results in active treatment group	Results in control group	p-value
Hoffman et al. 2002(19)	74	71%	Cranial/LV-GCA with angiography (83% TAB +)	- First relapse (6 months) - First relapse (12 months) -Treatment failure	68.9% (54.8-82.9) 74.8% (61.2-88.4) 57.5% (41.6-73.4%)	66.1% (50.2-82) 91.3% (80.6-100) 77.3% (61.9-82.8)	 0.31 0.26
Jover et al. (20)	78±8.7	66.7% vs 71.4%	TAB+ GCA	-Total relapse -Cumulative GC dose	9 (45%) 4187±1529	16 (84.2%) 5489.5±1396	0.018 0.009
Spiera et al. 2001 (21)	72±7 (I) 74±8 (C)	75% vs 56%	Cranial/LV-GCA (78-83% TAB+)	1)Cumulative GC dose -N weeks GC	6469±2024 68 23	5908±2131 60 25	0.6 0.5 0.6

				completion. -Time to GC <10 mg/day			
Van der Veen et al. 1996 (22)	79.9 (range 53-84)	30	GCA/PMR or both	nsp -Time to remission -Median dose of GC -Relapse rate	48 (range 30-100) 2756 (2100-7087) 18	45 (range 22-104) 2747 (1452-5294) 15	nsp nsp nsp
Schaufelberger et al. 1998 (23)	75.7 vs 70.5	11 vs 9	GCA	-Accumulated dose of GC at 6 mo (g)	1.41	1.44	nsp
Schaufelberger et al. 2006 (24)	71.3±6.8 (I) vs 69.8±6.1 (C)	17 vs 21	GCA	-GC dose at end of study	Data not shown (significant reduction)	Data not shown (significant reduction)	nsp
Liozon et al. 1993 (25)	Median 75	nsp	GCA	-Total duration of GC	14 mo	13 mo	ns
				-Relapses during treatment	4	6	ns
				-Relapses after GC withdrawal	1	7	<0.02
				-Recovery > 1 year after discontinuation	8	2	<0.02
De Silva et al. 1986 (26)	69 vs 79	11 vs 13	GCA/PMR or both (11 TAB+), not distinguished	-GC dose 52 weeks	1.9±0.84	4.2±0.58	<0.05

1.2.1.5 Supplementary Table 18. Methotrexate and other csDMARDs: safety/events

Study	Type of AE	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for
Hoffman et al. 2002 (19)	-Vision loss	18% entry + 8 (13.8%) new	4	4	na	na	na	na	na	na

	-Artery stenosis	2%			na	na	na	na	na	na
	-Cushingoid	98 (100%)	51	48	na	na	na	na	na	na
	-Fractures	3	2	1	na	na	na	na	na	na
	-Serious infections	3	1	2	na	na	na	na	na	na
	-MTX withdraw AE	3 (↑LFT,fever,↓PLT)	3	0	na	na	na	na	na	na
	-Deaths	3	2	1	na	na	na	na	na	na
Jover et al. 2001 (20)	-Vision loss	14 (33%) at entry, 0 new	0	0	na	na	na	na	na	na
	-Cataracts		2 (10%)	1 (5.2%)	na	na	na	na	na	na
	-Diabetes mellitus		3 (15%)	7 (36.8%)	na	na	na	na	na	na
	-Hypertension		12 (60%)	16 (84.2%)	na	na	na	na	na	na
	-Cushingoid		3 (15%)	6 (31.8%)	na	na	na	na	na	na
	-Fractures		4 (20%)	2 (10.5%)	na	na	na	na	na	na
	-Infections		8 (40%); 1 serious	10 (52.6%)	na	na	na	na	na	na
	-MTX withdrawal AE	3 (↓WBC+↓Hb+mucositis, pancytopenia, oral ulcers)	3	0	na	na	na	na	na	na
	-Deaths	0	0	0	na	na	na	na	na	na
Spiera et al. 2001 (21)	-Vision loss	3 at study entry, no new cases	0	0	na	na	na	na	na	na
	-Cataracts		0	0	na	na	na	na	na	na
	-Cushingoid		3	3	na	na	na	na	na	na
	-Fractures		1	3	na	na	na	na	na	na
	-Infections		6	4	na	na	na	na	na	na
	-Malignancy		2	1	na	na	na	na	na	na
	-MTX withdrawal AE		0	0	na	na	na	na	na	na
	-Deaths		0	0	na	na	na	na	na	na
Van der Veen et al. 1996 (22)	-Vision loss	None	0	0	na	na	na	na	na	na
	-Hypertension		9	5	na	na	na	na	na	na
	-Hyperglycaemia		5	7	na	na	na	na	na	na
	-↑ body weight		14	11	na	na	na	na	na	na
	-Fractures		1	2	na	na	na	na	na	na
	-Infections		5	2	na	na	na	na	na	na
	-Malignancy	3	0	3	na	na	na	na	na	na

	-MTX withdrawal AE -Deaths	Abnormal liver tests 6	1		na na	na na	na na	na na	na na	na na
Schaufelberger et al. 1998 (23)	Not assessed in detail by study	na	na	na	na	na	na	na	na	na
Schaufelberger et al. 2006 (24)	AE	26/29 in intervention group	na	na	na	na	na	na	na	na
Liozon et al. 1993 (25)	Severe AE	12.5%	na	na	na	na	na	na	na	na
De Silva et al. 1986 (26)	-Nausea	na	4	2	na	na	na	na	na	na
	-Diarrhoea	na	1	1	na	na	na	na	na	na

1.2.1.6 Supplementary Table 19. Methotrexate and other csDMARDs: risk of bias assessment (Cochrane bias tool for RCT)

Study	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of participants and personnel (performance bias)**	**Blinding of outcome assessment (detection bias) (patient-reported outcomes)**	**Blinding of outcome assessment (detection bias) (all-cause mortality)**	**Incomplete outcome data (attrition bias) (short-term 2-6 weeks)**	**Incomplete outcome data (attrition bias) (long-term > 6 weeks)**	**Selective reporting (reporting bias)**
Hoffman et al. 2002 (19)	Low	Low	Low	Low	Low	Unclear	Unclear	Unclear
Jover et al. 2001 (20)	Low	Low	Low	Low	Low	Low	Low	Low
Spiera et al. 2001 (21)	High	High	Unclear	Low	Low	Low	Low	Low
Van der Veen et al. 1996 (22)	High	High	Low	Unclear	Unclear	Low	Low	High

Schaufelberger et al. 1998 (23)	High	High	High	High	High	High	High	High
Schaufelberger et al. 2006 (24)	High	High	High	High	High	High	High	High
Liozon et al. 1993 (25)	High	High	High	High	High	High	High	Low
De Silva et al. 1986 (26)	High	High	Low	Unclear	Unclear	High	Unclear	High

1.4.2 OBSERVATIONAL STUDIES (MTX and other csDMARDs)

1.4.2.1 Supplementary Table 20. Methotrexate and other csDMARDs: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Methotrexate						
Retrospective						
Leon et al. 2017 (27)	Observational, retrospective, longitudinal study	4	Long-term continuation MTX in clinical practice	GCA pts treated with MTX (new diagnoses and relapses)	na	2014
Cyclophosphamide						
Retrospective						
De Boysson et al. 2013 (28)	Retrospective case series (15 pts) + systematic literature review	4	Effectiveness of Cyc for GCA	GCA satisfying ACR criteria, initially responding to GC but then needed GC for long term at moderate-to high-dose or had serious side effects → led to **Cyc as steroid-sparing agent**;	Stated in inclusion criteria	nsp

				no other conditions (malignancy, infections, other inflammatory disease), fu of at least 1 year after last Cyc pulse. Previous csDMARD: MTX (n=4), hydroxychloroquine (n=2), dapsone (n=1), thalidomide (n=1), GC-toxicity (73%)		
Loock et al. 2012 (29)	Retrospective cohort, 3 centres (35 pts)	4	Efficacy and safety of Cyc for remission induction in **GCA with persistent disease activity despite GC+** csDMARD	Pts not satisfying ACR/Chapel Hill criteria included if all of the following: 1) very suggestive clinical features of disease: concomitant PMR and/or constitutional symptoms (fever, weight loss, night sweats) or evidence cranial and/or limb ischaemia + ↑ ESR≥50 mm/h and response to GC (at least 20 mg/day prednisolone equiv); 2) Pt >50 at onset 3)Typical imaging of thoracic aorta and/or proximal large arteries; 4) no other disease found accountable.	Ongoing or recent < 2 years malignancy	January 2004-December 2009
Quartuccio et al. 2012 (30)	Retrospective cohort, monocentric (19 pts)	4	Efficacy of Cyc as **steroid-sparing** agent in GCA	Newly diagnosed (n=4, with diabetes) or refractory GCA to GC+/- MTX (n=15) fulfilling ACR criteria treated with Cyc. -Resistance to GC: persistence of both symptoms and ↑ APR after induction with 1 mg/kg/day or disease relapse during high- to medium-dose GC (0.3-1 mg/kg/day PRED) and unacceptable risk of GC toxicity (diabetes, severe osteoporosis with fractures,	nsp	2003-2011

				uncontrolled hypertension, ischaemic cardiopathy, cerebrovascular events)		
GCA + PMR						
Retrospective						
LEFLUNOMIDE						
Adizie et al. 2012 (31)	Case series, retrospective (23 pts, 9 with GCA)	4	Efficacy and safety of LEF in GCA or PMR with **difficulties in tapering GC**	GCA fulfilling ACR criteria or PMR fulfilling consensus criteria Previous MTX (n=3)	nsp	nsp

1.4.2.2 Supplementary Table 21. Methotrexate and other csDMARDs: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Leon et al. 2017 (27)	MTX discontinuation due to: a) adverse drug reaction (ADR); b) inefficacy as rheumatologist criteria; c) patient decision; d) sustained clinical response as rheumatologist criteria; e) other medical causes.		Rheumatologist (clinical)	-Kaplan Meyer, cox multivariate regression	nsp
De Boysson et al. 2013 (28)	Report on effectiveness of Cyc to treat **GC-dependent GCA**	-GC dependence: PRED dose of 420 mg/day for 6 months or 410 mg/day for 1 year in order not to relapse.	Computerized patient-record system	Standard statistics	nsp

		-Response to Cyc: improved clinical and biological findings. -Remission: sustained absence (412 months) of active signs of vasculitis at a daily GC dose <7.5 mg.			
Loock et al. 2012 (29)	Response at the time of Cyc discontinuation	-Response: substantial improvement (clinical/imaging) as estimated by radiologist and treating physician + GC<10 mg prednisolone/day (or by >50% of the dose prior to Cyc) -Refractory disease: persistently active or progressive disease requiring GC≥10 mg/day in spite of adjunctive csDMARD (MTX, AZA, LEF) for at least 3 mo. Or < 3 mo if side effects or contraindicated -Remission: no signs of active vasculitis (clinical, imaging if available, ESR≤20 mm/g) + GC<7.5 mg/day	Treating physician, radiologist, clinical records	Wilcoxon test	nsp

		-Relapse: reoccurrence of significant signs active vasculitis (clinical and or imaging and or ESR>40 mm/h + requiring sustained ↑ GC>10 mg/day for more 4 weeks and/or escalation of csDMARD			
Quartuccio et al. 2012 (30)	Efficacy of Cyc as steroid-sparing agent in GCA	-Efficacy: complete disappearance of GCA symptoms + normalization of APR -Relapse: both recurrence of GCA symptoms and/or PMR + positive APR	Rheumatologist/clinical records	Standard methods	nsp
Adizie et al. 2012 (31)	-Efficacy	-Response confirmed at least at 2 consecutive visits:1) >70% patient global improvement; 2) normal CRP and 3) >50% GC reduction -Complete response: 3/3 criteria -Partial response: ≤1/3	Rheumatologist	nsp	nsp

1.4.2.3 Supplementary Table 22. Methotrexate and other csDMARDs: intervention/treatment characteristics

Study ID	Follow-up duration	Patient-years	Overall n. of patients	Intervention	Control	Treatment group	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Leon et al. 2017 (27)	1991-2014	244 patient-years	108	MTX 10-15 mg/week	na	MTX 10-15 mg/week + average GC 50 mg/d at diagnosis	Up to 8.4 years	nsp	nsp	Aspirin (36%) Statin (21%)
De Boysson et al. 2013 (28)	43 mo (range 14-75)	nsp	15	GC + i.v. Cyc	na	GC (median 20 mg/day range 7.5-35) + i.v. Cyc -500 mg/m^2 (700-1000 mg per pulse) (n=13) -500 mg fixed dose (CKD or age 76 years with poor health) (n=2) -3 infusions 2-weekly then monthly (n=5) -monthly infusions n=10) for a median of 6 pulses. + maintenance treatment at 1 mo with MTX (0.3 mg/kg/week) (n=3)	Median 5 mo (3-7)	nsp	nsp	nsp

Loock et al. 2012 (29)	Mean 49 mo (at least 12 after Cyc discontinuation)	nsp	35→ data on 31	GC + Cyc i.v. or p.o.	na	GC (30.9±35.3 mg/day)→ csDMARD (MTX, AZA or LEF) → Cyc i.v. (60%) 15.8±6.4 mg/kg body weight every mean 23.1±4 days for men n of infusions 7.5±2.7; p.o. (23%) 1.6±0.4 mg/kg body weight for 23.9±15.4 weeks → maintenance tx (MTX 54%, AZA 29%, LEF 7%, GC only 4%)	Mean 7.5 mo of i.v., mean 23.9 weeks for p.o.	Maintenance treatment with csDMARD or GC; Cyc discontinued (not specified)	Rechallenge with Cyc	i.v. GC (100 mg) and 5-HT3 receptor blockade for antiemetic prior to each Cyc infusion.
Quartuccio et al. 2012 (30)	Range 1mo-9 years after Cyc	nsp	19	GC + Cyc p.o.	na	GC (0.3-1 mg/kg/day prednisone or equivalents) for at least 2 weeks in resistant/relapsing or low-medium GC (<0.3 mg/kg/day PRED) in pts with high risk of GC-side effects + Cyc p.o. 1.5-2 mg/kg/day for	3-12 mo (until clinical disappeared and lab inflammatory tests normalized, for max 12 mo)	After Cyc suspension→ maintenance with MTX 10-20 mg/week	nsp	Anti-platelet or anticoagulant already ongoing (n=17/19) or started at GCA diagnosis (2/19) Concomitant daily oral mesna (diluted in juice, with 1:1 ratio with Cyc)

						3-12 mo (dose reduced by 25% if GFR<60 ml/min or >65 years. Concomitant daily oral mesna (diluted in juice, with 1:1 ratio with Cyc) → MTX 10-20 mg/week				
Adizie et al. 2012 (31)	nsp	nsp	9 (GCA) + 14 (PMR)	LEF 10 mg/day p.o. → 10/20 alternate days (n=5) or 20 mg/day (n=2)	na	GC + LEF 10 mg/day p.o. → 10/20 alternate days (n=5) or 20 mg/day (n=2)	nsp	nsp	nsp	nsp

1.4.2.4 Supplementary Table 23. Methotrexate and other csDMARDs: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Disease duration at treatment start	Primary outcome	Results in active treatment group	Results in control group	p-value
Leon et al. 2017 (27)	76.6±6.5	88 (81.5%)	58% TAB+	28 days (50%) 2 months (70%) 5.7 months (remaining)	-IR of MTX discontinuation	37.26 (30.3-45.7)	na	na
De Boysson et al. 2013 (28)	67 years (range 55–83)	13	GCA (53% TAB+) LV-GCA (n=4)	11 mo (4-121)	-Remission	9/15 (53%). Twelve (80%)	na	na

					-Relapse	6/15 (40%) at 6 (3–36) mo after last Cyc infusion	na	na
					-Relapse following remission	7/13 (54%)	na	na
					-Remission with stopped GC and MTX	2/16 (25%)	na	na
					-Progressive disease	3/16 (19%)	na	na
Loock et al. 2012 (29)	65.3±7.7	27 (77%)	GCA (60% TAB+) LV-GCA (n=24)	nsp	-Response	28 (90.3%) (LV-GCA 86.4%/ACR+ 88%)	na	na
					-Remission	8 (25.8%) (LV-GCA 31.8%/ACR+ 24%)	na	na
					-Treatment failure	3 (9.7%) (LV-GCA 13.6%/ACR+ 12%)	na	na
					-Mean GC reduction	-13.1 mg (-51.5%)	na	<0.001
					-Relapse	12 (42.9%) after 20.5 mo		
Quartuccio et al. 2012 (30)	70.11±7.94	16	GCA	nsp	-Remission	15/19	na	na
					-Sustained remission after Cyc discontinuation (6-12 mo after Cyc)	12/13	na	na
					-GC suspended	6/15	na	na
					-Relapse	4/15 >12 mo after Cyc suspension	na	na
					- Immunohistochemical analysis of IL17 and IFNγ on TAB	IFNγ producing T-lymphocytes baseline 77.8%, IL17 66.7%. One pt had repeated TAB after 3 mo: disappearance of inflammatory infiltrate	na	na
Adizie et al. 2012 (31)	73 (range 64-81) in GCA	16	GCA, LV-GCA, PMR	3 years (range 1-10) for GCA	-Response (complete or partial)	9/9 of GCA	na	na

1.4.2.5 Supplementary Table 24. Methotrexate and other csDMARDs: safety/events

Study ID	Type of AE	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for	Predictors/associated factors
Leon et al. 2017 (27)	-MTX discontinuation:	91	91	na	37.26 (30.3-45.7)	na	na	na	na	na	-inefficacy: younger age, baseline CV, higher dose GC, lower starting dose MTX -ADR: older age, COPD, higher baseline ESR, clinical presentation, higher max dose MTX -Sustained response: inversely with older pts, higher n flares
	a) ADR	51	51	na	20.8 (15.8-27.4)						
	Severe ADR	4	4	na	1.6 (0.6-4.36)						
	ADR infections	31	31	na	12.6 (8.9-18)						
	b) sustained response	20	20	na	8.1 (5.3-12.7)						
	c)inefficacy	7	7	na	2.8 (1.3-6.0)						
	d)patient decision	7	7	na	2.8 (1.3-6.0)						
	e) other medical cause	7	7	na	2.8 (1.3-6.0)						
De Boysson et al. 2013 (28)	-AE	80%		na	na	na	na	na	na	na	Followed for at least 12 mo after last Cyc pulse
	-Cyc discontinuation	13%		na	na	na	na	na	na	na	na
	-Infections		1 (pneumocystis)	na	na	na	na	na	na	na	na
Loock et al. 2012 (29)	-AE	11 (33.3 %)	na	na	na	na	na	na	na	na	na
	-Haemorrhagic cystitis	1	na	na	na	na	na	na	na	na	na
	-Leucopenia	6	na	na	na	na	na	na	na	na	na
	-Infections	6	na	na	na	na	na	na	na	na	na

	-Death	3	na	na	na	na	na	na	na	na	na
Quartuccio et al. 2012 (30)	-AE	10	na	na	na	na	na	na	na	na	na
	-Cytopenias	3	na	na	na	na	na	na	na	na	na
	-Infections	1	na	na	na	na	na	na	na	na	na
	-Death	1 (hepatitis)	na	na	na	na	na	na	na	na	na
	-Cyc withdrawal	5	na	na	na	na	na	na	na	na	na
Adizie et al. 2012 (31)	-AE	na	2	na	na	na	na	na	na	na	na

1.4.2.6 Supplementary Table 25. Methotrexate and other csDMARDs: risk of bias assessment (Newcastle-Ottawa scale for cohort studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two ∗)
Leon et al. 2017 (27)	∗	na	no	∗	na	Self-report	∗	nsp	3
De Boysson et al. 2013 (28)	∗	na	∗	∗	na	nsp	∗	∗	5
Loock et al. 2012 (29)	∗	na	no	∗	na	Self-report	∗	∗	4
Quartuccio et al. 2012 (30)	∗	na	no	∗	na	Self-report	∗	∗	4
Adizie et al. 2012 (31)	nsp	na	nsp	∗	na	Self-report	nsp	∗	2

1.4.3 META-ANALYSIS (MTX and other csDMARDs)

1.2.3.1 Supplementary Table 26. Methotrexate and other csDMARDs: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	End of follow-up for analysis	Included studies
GCA						
METHOTREXATE – Meta-analysis						
Mahr et al. 2007 (32)	Meta-analysis of 3 RCT	1a	Efficacy and safety adjunctive MTX for newly diagnosed GCA	Newly diagnosed GCA	1966-2006	Jover et al. (20) Spiera et al. (21) Hoffman et al. (19)
ADJUNCTIVE IMMUNOSUPPRESSION (csDMARD or bDMARD) – Meta-analysis						
Yates et al. 2014 (33)	Meta-analysis of RCT (parallel-group RCT of at least 16 weeks with at least 20 participants) (10 RCT)	1a	Efficacy (relapse rate) and safety of prednisolone alone or combined with adjunctive immunosuppressive agent (csDMARD or bDMARD) for GCA	GCA TAB+, satisfying ACR criteria parallel-group RCT of at least 16 weeks with at least 20 participants. Intervention: alternative adjunct immunosuppressant, alternative GC dosing or routes Outcome on relapse rates or rates of infections	1946-August 2013	-3 RCT: comparison different GC regimens -3 RCT: comparison prednisolone to MTX -4 RCT: comparison prednisolone to dapsone, IFX, ADA, HCQ

1.2.3.2 Supplementary Table 27. Methotrexate and other csDMARDs: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Mahr et al. 2007 (32)	Time to first relapse, time to second relapse, number of patients needed to be treated to prevent a first or second relapse, cumulative dose of GC, time to	As defined in single trials	Rheumatologist	Cox-proportional hazard models -Heterogeneity on length of follow-up	nsp

	sustained discontinuation of GC, adverse events.				
Yates et al. 2014 (33)	Efficacy and safety of different GC regimens or adjunctive immunosuppressant in GCA	As defined in single trials	Rheumatologist	Fixed effect model, if heterogeneity detected random effects model, different lengths of follow-up, n of relapses modelled in Poisson regression	nsp

1.2.3.3 Supplementary Table 28. Methotrexate and other csDMARDs: intervention/treatment characteristics

Study ID	Follow-up duration	Overall n. of patients	Active treatment group	n. of patients	Control group	n. of patients	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Mahr et al. 2007 (32)	54.7±39.2	161	MTX (7.5-15 mg/week p.o.)	84	Placebo	77	96 weeks	nsp	nsp	nsp
Yates et al. 2014 (33)	Not pooled	638	-Iv GC -Alternate day GC -MTX -Dapsone -HCQ -ADA -IFX	164-27 60 21+42+98 48 64 70 44	Immunosuppressant vs GC or other GC regimen	Not pooled	Not pooled	nsp	nsp	nsp

1.2.3.4 Supplementary Table 29. Methotrexate and other csDMARDs: population characteristics and control and comparison

Study ID	Age	% females	GCA subtype	Primary outcome	Results in active treatment group	Results in control group	p-value
Mahr et al. 2007 (32)	74.6±8	113 (70%)	Cranial, LV-GCA, ischaemic. Newly diagnosed	-Hazard ratio for first relapse	0.65 (95%CI 0.44-0.98)	na	0.004
				-Hazard ratio for second relapse	0.49 (95%CI 0.27-0.89)	na	0.02

				-Number needed to treat to prevent 1st relapse	3.6 pts (95%CI 2.2-56.8)	na	na
				-Number needed to treat to prevent 2nd relapse	4.7 pts (95%CI 3.3-21.9)	na	na
				-Reduction in GC cumulative dose	Reduced by 842 mg by week 48	na	<0.001
				-Hazard ratio for achieving GC discontinuation for ≥ 24 weeks	2.84	na	0.001
Yates et al. 2014 (33)	73	72%	GCA TAB+ (83%)	-Relapse rate	GC control arms: 27.9-92.3%. Relapse rate for studies > 18 mo of follow-up: 71.0-92.3% <12 mo 27.9-92.0%. No association between relapse rate and starting GC dose, dose at day 60 or total GCs dose.	na	na

1.2.3.5 Supplementary Table 30. Methotrexate and other csDMARDs: safety/events

Study ID	Type of AE/event/outcome	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	p-value	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for
Mahr et al. 2007 (32)	-Fractures	13 (8%)	7 (8%)	6 (8%)				0.90			
	-Diabetes	13 (8%)	4 (5%)	9 (12%)				0.11			
	-Infection	35 (22%)	17 (20%)	18 (23%)				0.63			
	-Abnormal liver function	28 (17%)	14 (17%)	14 (18%)				0.80			
	-Thrombocytopenia	6 (4%)	4 (5%)	2 (35)				0.68			
	-Leukopenia	1 (1%)	1 (2%)	0				1			
	-Malignancy	6 (4%)	4 (5%)	2 (3%)				0.68			
Yates et al. 2014 (33)	**-Relapse**										

	Iv GC	nsp	27	31	nsp	RR	0.78 (95%CI 0.54-1.12)	nsp	na	na	na
	Alternate day GC	nsp	14	4	nsp	RR	3.50 (95%CI 1.39-8.80)	nsp	na	na	na
	MTX	nsp	46	50	nsp	RR	0.85 (95%CI 0.66-1.10)	nsp	na	na	na
	Dapsone	nsp	5	13	nsp	RR	0.37 (95%CI 0.16-0.87)	nsp	na	na	na
	HCQ	nsp	20	14	nsp	RR	1.43 (95% CI 0.89-2.30)	nsp	na	na	na
	ADA	nsp	14	18	nsp	RR	0.82 (95%CI 0.49-1.38)	nsp	na	na	na
	IFX	nsp	16	8	nsp	RR	1.14 (95%CI 0.64-2.05)	nsp	na	na	na
	- **Infections**										
	Iv GC	nsp	23	13	nsp	RR	1.58 (95%CI 0.90-2.78)	nsp	na	na	na
	Alternate day GC	na			nsp			nsp	na	na	na
	MTX	nsp	15	16	nsp	RR	0.85 (95%CI 0.49-1.47)	nsp	na	na	na
	Dapsone	nsp	1	1	nsp	RR	0.96 (95%CI 0.06-14.43)	nsp	na	na	na
	HCQ	na			nsp			nsp	na	na	na
	ADA	nsp	34	36	nsp	RR	1.93 (95%CI 1.09-3.39)	nsp	na	na	na

	IFX	Stopped early because of infections	29	9	nsp	RR	1.27 (95%CI 0.78-2.08)	nsp	na	na	na

1.2.3.6 Supplementary Table 31. Methotrexate and other csDMARDs: risk of bias assessment (AMSTAR tool)

Study ID	Was a priori design provided?	Duplicate study selection and data extraction?	Comprehensive literature search performed?	Status of publication (grey literature) used as inclusion criteria?	List of studies provided?	Characteristics of the studies provided?	Scientific quality of the included studies assessed and documented?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies appropriate?	Likelihood of publication bias assessed?	Conflict of interest included?
Mahr et al. 2007 (32)	No	Can't answer	Yes	Can't answer	Yes	Not applicable	Not applicable	Not applicable	Yes	No	Yes
Yates et al. 2014 (33)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

1.5 THE ROLE OF TOCILIZUMAB AND OTHER BIOLOGIC IMMUNOSUPPRESSIVE DRUGS

1.3.1 RANDOMISED CONTROLLED TRIALS (TCZ and other bDMARD)

1.3.1.1 Supplementary Table 32. Evidence retrieved for the use of Tocilizumab and other biologic immunosuppressive drugs (bDMARDs): overview of included studies

Study ID	Study design	Level of evidence	Intervention overview	Inclusion criteria	Exclusion criteria
GCA					
Tocilizumab					
Stone et al. 2017 (34)	Multicentric, double-blind, placebo controlled randomised controlled trial (GIACTA)	1b	Efficacy and safety of two TCZ s.c. schemes and two GC tapering on GCA (newly diagnoses and relapsing)	**Newly diagnosed or relapsing GCA** (TAB+) **or LV-GCA** (angiography/CT/MRI or PET-CT)	Iv GC >100 mg <6 days before baseline, other immunosuppressive drugs, recent major surgery, MTX < 6 weeks, GC for other condition than GCA, serious uncontrolled concomitant disease, history of diverticulitis, IBD, GI conditions predisposing to perforation, infections, malignancy (except skin carcinoma or cervix uteri cured)
Villiger et al. 2016 (35)	Phase 2, randomised, double-blind, placebo-controlled trial	1b	TCZ i.v. for induction and maintenance of remission in GCA (newly diagnosed or relapsing)	**Newly diagnosed** (23/30) **(80% vs 70%) or relapsing GCA** (TAB+) **or LV-GCA** (MRA) satisfying ACR criteria, > 50 years. Umorally active (ESR ≥ 40 mm/h and CRP≥20 mg/L). Between 2012-2014	Uncontrolled concomitant health problems, active infection, any disease requiring GC. Previous treatment with bDMARD. Maximum 10 days of prednisolone 1 mg/kg allowed between inclusion and first infusion.
Abatacept					
Langford et al. 2017 (36)	Multicentric, double-blind, placebo controlled, randomised controlled trial	1b	Efficacy of ABA i.v. in GCA (newly diagnosed or relapsing)	**Newly diagnosed** (60% vs 52%) **or relapsing** (40% vs 48%) **GCA or LV-GCA** (MRI) with active disease within previous 2 mo (25 TAB+)	Active infections, chronic infections (TB, HBV, HCV, HIV), cytopenias, pregnancy, recent live vaccination, neoplasm except for skin or solid tumor treated with absence of disease for at least 5 years, previous treatment with GC or bDMARD

TNFi					
Adalimumab					
Seror et al. 2014 (37)	Multicentric, double-blind, placebo controlled, randomised controlled trial HECTHOR (Humira* pour l'Epargne CorTisonique dans la maladie de HORton).	1b	Steroid-sparing effect of early addition of 10-week course of ADA in GCA (newly diagnosed)	**Newly diagnosed GCA,** according to ACR criteria > 50 years. TAB+ for the first part of the protocol, then eligible even if TAB-fulfilling Hunder criteria	GCA-related visual symptoms >1mg/kg GC <14 days before randomization. Previous TNFi or immunosuppressive drugs, serious or chronic infections < 30 days, antibiotics < 14 days, neoplasms < 5 years (except skin), history moderate/severe congestive heart failure or demyelinating disease, recent stroke, active TB or latent TB (TST > 5mm or IGRA), active chronic HBV, HCV, HIV.
Etanercept					
Martinez-Taboada et al. 2008 (38)	Multicentric (4 centres), double-blind, placebo controlled, randomised controlled trial	1b	Ability to withdraw GC therapy and control disease activity at 12 mo with ETA in GCA pts with AE to GC.	**GCA (TAB+) controlled with stable GC (≥10 mg/day PRED previous 4 weeks) but with at least one GC-related AE:** 1) GC-induced DM or impaired glucose tolerance; 2) osteoporosis defined by densitometric criteria or fracture; 3) High blood pressure (systolic > 140 mmHg, diastolic > 90 mmHg or need for therapy.	GCA not biopsy proven, chronic HBV, HCV, HIV, TB or fungal infections, malignancy < 5 years, multiple sclerosis or other demyelinating disorders, cytopenia, other contraindications to ETA.
Infliximab					
Hoffman et al. 2007 (39)	Multicentric (22 centres), randomised, double-blind, placebo-controlled trial	1b	If adjunctive IFX after achieving remission with GC reduces relapses, cumulative GC dose, GC-related AE	**Newly diagnosed GCA satisfying ACR criteria ≤ 4 weeks,** ESR ≥ 40 mm/h at diagnosis, **in clinical remission**	GCA or PMR > 4 weeks, no response to GC within 5 days, i.v. GC, other csDMARD, bDMARDs, lab abnormalities contraindicating IFX, serious or chronic infections < 3 mo, opportunistic infections < 6 mo, cancer < 5 years, congestive heart failure, demyelinating disease, uncontrolled medical condition

1.3.1.2 Supplementary Table 33. Tocilizumab and other bDMARDs: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Stone et al. 2017 (34)	1)Rate of sustained GC-free remission at week 52 vs placebo+26-week GC taper 2)Rate of sustained GC-free remission at week 52 vs placebo+52-week, cumulative GC dose, flare incidence after remission, quality of life, safety	1)Flare: recurrence of signs/symptoms of GCA or ESR elevation ≥30 mm/h attributable to GCA with the necessity for ↑ GC dose. -Remission: absence of flare and the normalization of CRP < 1 mg/dl. - Sustained remission: remission from week 12 through week 52 and adherence to the prednisone taper. 2)Toxicity	Dual-assessor (laboratory assessor, efficacy assessor)	Sensitivity analysis to exclude requirement for a normalized CRP from definition pf sustained remission.	Yes, at withdrawal and if no flares occurred
Villiger et al. 2016 (35)	1)Complete remission at a prednisolone dose of 0.1 mg/kg/day at week 12 2)Relapse-free survival at week 52 -Time to first relapse after remission -Cumulative GC dose	-Complete remission: no sign/symptoms of GCA, and normal ESR and CRP at prednisolone dose of 0.1 mg/kg/day. -Relapse: re-increase in ESR from <20 mm/h to ≥ 40 mm/g, and of CRP from normal to ≥10 mg/l + at least one: 1) symptoms of GCA (new or recurred headache, scalp or TA tenderness or pain, new or recurrent claudication, new/recurrent/worse TA signs and symptoms, TIA, MRA abnormalities, PMR, daily fever > 38°C >1 week.	Study assessor	Intention to treat, Kaplan Meyer. All randomised pts received drug/placebo	Intention to treat. If no completion of fu regarded as flaring

		-Major relapse: if cranial symptoms -Minor relapse: all others			
Langford et al. 2017 (36)	Duration of remission (relapse-free survival rate)	-Remission: absence of disease activity (sustained fever > 38°C >1 week, carotidynia, scalp tenderness, TA abnormalities, headache, ischemic retinopathy, optic retinopathy, visual loss, tongue/jaw pain and/or claudication, TIA, stroke, extremity claudication, signs/symptoms attributed to GCA necessitating reinstitution or increase in GC/or MSK symptoms or fatigue/malaise + ESR >40 mm/h or CRP↑) / imaging active disease: new vascular stenosis/aneurysm in new vascular site(MRI, CT, arteriography). -Relapse: presence of disease activity	Site investigator and study PI	Intent to treat analysis. Kaplan-meier curves	After discontinuation study drug follow-up weeks 4,12,24
Seror et al. 2014 (37)	1)Percentage of patients in remission with < 0.1 mg/kg/day prednisone at week 26 2)Decrease of GC in the first 6 mo -relapse-free at 1 year -safety	-Remission: disappearance of clinical symptoms and CRP < 15 mg/L. -Relapse: reappearance of GCA-related clinical symptoms or increase of CRP > 15 mg/L at 2 time points 1 week apart.	Study personnel /Rheumatologist	Intention to treat Logistic regression model with random effects	If GC dose at 26 weeks not known, considered non-responder

Martinez-Taboada et al. 2008 (38)	1)Ability to withdraw GC and control disease at 12 mo 2)GC cumulative dose -number of relapses during active phase -new side effects or worsening of previous GC-side effects -n relapses during 3 mo fu	-Relapse: symptoms and/or signs of GCA + elevations in at least one of the APR	Rheumatologist	Intent to treat; Standard statistics	nsp
Hoffman et al. 2007 (39)	1) Relapse-free rate through week 22 and AE 2)Proportion of patients who remained relapse-free through week 54, time to first relapse, level of markers of inflammation and disease activity, cumulative GC dose	-Disease relapse: increase in ESR from normal to ≥ 40 mm/h + at least 1 symptom/sign of GCA (sustained fever > 1 weeks, new or recurrent headache, pain or tenderness of the scalp, new, recurrent or worsening ischemic retinopathy, optic neuropathy, visual loss, new or recurrent pain or claudication of the tongue or jaw, new or recurrent claudication of the extremities, thickness tenderness or ulcers or nodules over TA or occipital arteries, worsening angiographic abnormalities compatible with vasculitis of aorta or primary branches, TIA or stroke, PMR -Clinical remission: ESR ≤ 40 mm/h without symptoms or signs of GCA	Rheumatologist (clinician investigator, physician assessor)	Intent to treat; Standard statistics	nsp

		-Complete clinical remission: clinical remission for 12 weeks after GC discontinuation			

1.3.1.3 Supplementary Table 34. Tocilizumab and other bDMARDs: intervention

Study ID	Follow-up duration	Overall n. of patients	Active treatment group	n. of patients	Control group	n. of patients	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Stone et al. 2017 (34)	1 Year (enrolled July 2013-April 2015)	251	- 26-week taper GC (doses between 20-60 mg/day) + -TCZ 162 mg/week s.c. or -TCZ 162 mg/2 weeks s.c.	251 (100 TCZ/week; 50 TCZ/2 weeks/50 placebo 26-week taper; 51 placebo 52-week taper)	-26-week taper GC/ or 52-week taper GC + placebo	101	52 weeks	26 and 52-week GC taper, reduce to 35 mg/day by 1 month, 20 mg by week 7, then differentiated tapers.	Switched to open-label escape therapy with prednisone + continuing TCZ/placebo	na
Villiger et al. 2016 (35)	52 weeks	30	-GC 1 mg/kg p.o. (prednisolone) + i.v.TCZ 8 mg/kg/4 weeks	20	placebo	10	52 weeks	GC taper weekly by 0.1 mg/kg/day until week 8, then by 0.05 mg/kg/week → 0.1 mg/kg by week 12. Then by 1 mg per day every month to 0 mg.	-Minor relapse: previous dose of GC + 10 mg/day; if good clinical response within 72 h continued for 2 weeks then tapered. -Major relapse: GC induction scheme reapplied.	ASA 100 mg/day, pantoprazole 40 mg/day, calcium 1000 mg/day, vit D 800 u/day, Ibandronate i.v. 3 mg every 3 months
Langford et al. 2017 (36)	12 months after enrollment of last patient	49 → 41 reached randomisation at week 12	-GC 40-60 mg/day with 28-week taper GC + i.v. ABA 10 mg/kg on	20	-GC 40-60 mg/day with 28-week taper GC + placebo	21	12 mo	28-week GC taper in both groups, reaching 20 mg/day by week 12.	Stop ABA/placebo	nsp

	(enrollment 2009-2014)		day 1,15, 29 and week 8 → at week 12 if in remission: randomize to -ABA/monthly -placebo							
Seror et al. 2014 (37)	52 weeks	70	GC (prednisone) 0.7 mg/kg/day + ADA s.c. 40 mg/2 weeks (week 0,2,4,6,8,10)	34	-GC (prednisone) 0.7 mg/kg/day + placebo	36	10 weeks	Taper by 0.1 mg/kg/day every 2 weeks up to week 8 to 0.3 mg/kg/day → 0.25 mg/kg week 10, 0.2 mg/kg week 12, 0.15 mg/kg week 14, 0.125 mg/kg week 20, 0.1 mg/kg week 24, decrease by 1 mg/day/4 weeks from week 28 until stop.	Increase GC to previous dose for 4 weeks, if persistent active disease or relapse GC schedule left to physician	All: ASA 80-250 mg/day during first 3 mo + PPI - bisphosphonate once a week + vit D (400 u/day) + calcium 1000 mg.
Martinez-Taboada et al. 2008 (38)	12 mo (active treatment: phase 1) + 3 mo (fu: phase 2)	17	GC (PRED) stable for at least 1 mo, ≥ 10 mg/day + ETA 25 mg /twice week s.c.	8	GC (PRED) stable for at least 1 mo, ≥ 10 mg/day + placebo	9	12 mo	a) If GC (PRED) >30 mg/day taper by 10 mg/weekly until 30 mg/day; b) 30 to 15 mg/day, taper by 5 mg/weekly; I 0 to 15 mg/day, taper by 2.5 mg/weekly.	-first relapse: PRED raised for 1 month to previous dosage able to control the disease activity → taper resumed. -second relapse: PRED again raised for 1 month to previous dosage able	Isoniazid 300 mg/day for 9 mo or riphampicin 600 mg/day for 4 mo in latent TB Patient's medications for comorbidities

									to control disease activity, and then tapered at half the dosage on the same schedule. -third relapse, withdrawn from the study	
Hoffman et al. 2007 (39)	At least 22 weeks	44	-GC (40-50 mg/day or 51-60 mg/day) + IFX (5 mg/kg) weeks 0,2,6 then every 8 weeks	28 (24 completed)	-GC+placebo	16 (15 completed)	22 weeks	GC tapered by 10 mg→ 20 mg/day then by 2.5 mg to 1 mg/day then by 1 mg to 0 mg/day	Resume previous dose + 10 mg/day for 2 weeks (if relapse resolved within 72 hors) or further increase by 10 mg. If visual symptoms at least 40 mg/day or previous dose + 10 mg (whichever higher) or further increase if not resolved within 48 hours	nsp

1.3.1.4 Supplementary Table 35. Tocilizumab and other bDMARDs: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Primary outcome	Results in active treatment group	Results in control group	p-value
Stone et al. 2017 (34)	69.5±8.5 (TCZ/week) 69.4±8.2 (TCZ/2 weeks) 69.3±8.1 (26-week GC taper) 67.8±7.7 (52-week GC taper)	78 (78%) 35 (70%) 38 (76%) 37 (73%)	Cranial (TAB+ 57-72%) + LV-GCA (38-50%) Newly diagnosed (46-52%); Relapsing (48-54%)	-Sustained remission	56% (TCZ/week) 53% (TCZ/2 weeks)	14% (26-week GC taper) 18% (52-week GC taper)	<0.001 (for the comparisons of either active treatment with placebo)
				-Cumulative GC dose	1862 (TCZ/week) 1862 (TCZ/2 weeks)	3296 (26-week GC taper) 3818 (52-week GC taper)	<0.001 (for both comparisons)
				-Quality of life	Improve 4.1 (TCZ/week) 2.76(TCZ/2weeks)	Worse -0.28 (26-week GC taper) -1.49 (52-week GC taper)	0.002 (TCZ/week vs 52-week taper)
Villiger et al. 2016 (35)	71.3±8.9 vs 68.8±16.9	13 (65%) vs 8 (80%)	Cranial GCA (TAB+) + LV-GCA (MRA) Newly diagnosed (80% vs 70%); relapsing	-complete remission week 12	17 (85%)	4 (40%)	Risk difference: 45% (95%CI 11-79); p=0.0301
				-relapse-free survival week 52	17 (85%)	2 (20%)	Risk difference: 65% (95%CI 36-94); p=0.0010
				-time to first relapse	11 weeks	12 weeks	0.77
				-cumulative GC dose	43 mg/kg	110 mg/kg	0.0005
				-GC taper to 0 at end of the trial	16 (80%)	2 (20%)	risk difference: 60%, (95%CI 30–90) p=0.0041
Langford et al. 2017 (36)	63.5 (57.3-80.1) vs 71.5 (54.3-86.6)	80% vs 100%	**GCA or LV-GCA** (MR**I) (25 TAB+)**	-Relapse-free survival at 12 months	46%	31%	0.049

				-Median duration of remission	9.9 mo	3.9 mo	0.023
Seror et al. 2014 (37)	74.5 (69-78) vs 74.5 (67-80.5)	24 (70.6%) vs 28 (77.8%)	**Cranial GCA** (TAB+ and TAB-)	-Pts in remission on <0.1 mg/kg/day at week 26	20 (58.9%)	18 (50%)	OR 1.43; 95%CI 0.54-3.80; p=0.46)
				-GC dose 26 weeks	0.12 mg/kg ± 0.05	0.13 mg/kg ± 0.7	
				-Adjusted between group difference in GC dose at 26 weeks	-0.01 mg/kg/day (95%CI -0.07-0.05)		0.77
				-Adjusted between group difference in GC dose at 52 weeks	-0.02 (95%CI -0.10-0.07)		0.71
				-Relapse	20/27	26/35	
				-Time to relapse	Median 24 weeks (95%CI 17-31)	17 weeks (95%CI 11-29)	0.51
Martinez -Taboada et al. 2008 (38)	74.5±5.7 vs 74.4±6.8	75% vs 88.9%	**GCA** (TAB+)	-ability to withdraw GC and control disease activity at 12 mo	50%	22.2%	na
				-cumulative GC dose	1.5±1g	3±1.5 g	0.03
				-relapses during active phase study	50%	77.8%	ns
				-relapses during fu phase (stopped ETA)	1/5 (25%)	1/1 (100%)	ns
Hoffman et al. 2007 (39)	71.5 vs 60.5	4 (86%) vs 11 (69%)	**GCA** (83% TAB+)	-Relapse-free at 22 weeks	43%	50%	0.65

				-Proportion of patients who tapered to 10 mg/day without relapse	61%	75%	0.31

1.3.1.5 Supplementary Table 36. Tocilizumab and other bDMARDs: safety/events

Study	Type of AE/event	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age /gender aHR (I vs C)	aHR (I vs C)	Adjusted for
Stone et al. 2017 (34)	-Flares	N in each tx group	23% (TCZ/week) 26% (TCZ/2 weeks)	68% (26-week GC taper) 49% (52-week GC taper)	nsp	HR	0.23 (0.11-0.46) 0.28 (0.12-0.66); p<0.001	na	na	Compared to 26-week GC taper
	-Vision loss	N in each tx group	0 (TCZ/week) 1 (TCZ/2 weeks)	0 (26-week GC taper) 0 (52-week GC taper)	nsp	na	na	na	na	na
	-Serious AE	N in each tx group	15% (TCZ/week) 14% (TCZ/2 weeks)	22% (26-week GC taper) 25% (52-week GC taper)	Rate in each tx group	na	na	na	na	na
	-Serious infections	N in each tx group	7% (TCZ/week) 4% (TCZ/2 weeks)	4% (26-week GC taper) 12% (52-week GC taper)	nsp	na	na	na	na	na
	-Neutropenia	N in each tx group	4% (TCZ/week) 4% (TCZ/2 weeks)	nsp	nsp	na	na	na	na	na
	-↑ LFT	N in each tx group	2% (TCZ/week) 2% (TCZ/2 weeks)	nsp	nsp	na	na	na	na	na

	-AE withdrawal	N in each tx group	6% (TCZ/week) 6% (TCZ/2 weeks)	4% (26-week GC taper) 0 (52-week GC taper)	nsp	na	na	na	na	na
Villiger et al. 2016 (35)	-AE	N in each tx group	26 (75%)	23 (70%)	na	na	na	na	na	na
	-Serious AE	N in each tx group	7 (35%)	5 (50%)	na	na	na	na	na	na
	-GI disease	N in each tx group	4	1	na	na	na	na	na	na
	-GI perforations	N in each tx group	1 prepyloric ulcer	1 (undiagnosed diverticulosis)	na	na	na	na	na	na
	-fractures	N in each tx group	1	3	na	na	na	na	na	na
	-GC hyperglycaemia and myopathy	N in each tx group	3	3	na	na	na	na	na	na
	-infections	N in each tx group	10	1	na	na	na	na	na	na
Langford et al. 2017 (36)	-AE	129	nsp	nsp	na	na	na	na	na	na
	-serious AE	23	nsp	nsp	na	na	na	na	na	na
	-infections	33	nsp	nsp	na	na	na	na	na	na
	-Serious infections	2	nsp	nsp	na	na	na	na	na	na
	-cancer	3	1	1	na	na	na	na	na	na
Seror et al. 2014 (37)	-AE	nsp	24 (70.59%)	35 (97.22%)	na	na	na	na	na	na
	-Serious AE	nsp	5 (14.7%)	17 (47.2%)	na	na	na	na	na	na
	-Serious infections	nsp	3	5	na	na	na	na	na	na
	-Deaths	nsp	1 (pneumonia)	2 (septic shock and cancer)	na	na	na	na	na	na
Martinez-Taboada et al. 2008 (38)	-New GC related AE (DEXA, fractures, hypertension, diabetes)	No difference	nsp	nsp	na	na	na	na	na	na

	-Serious AE	nsp	3	3	na	na	na	na	na	na
	-Infections	nsp	4	4	na	na	na	na	na	na
Hoffman et al. 2007 (39)	-AE	nsp	71%	56%	Difference rate 15 percentage points (CI -14 to 45)	na	na	na	na	na

1.3.1.6 Supplementary Table 37. Tocilizumab and other bDMARDs: risk of bias assessment (Cochrane bias tool for RCT)

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias) (all-cause mortality)	Incomplete outcome data (attrition bias) (short-term 2-6 weeks)	Incomplete outcome data (attrition bias) (long-term > 6 weeks)	Selective reporting (reporting bias)
Stone et al. 2017 (34)	Low	Low	Low	Low	Low	Low	Low	Low
Villiger et al. 2016 (35)	Low	Low	Low	Low	Low	Low	Low	Low
Langford et al. 2017 (36)	Low	Low	Low	Low	Low	Low	Low	Unclear
Seror et al. 2014 (37)	Low	High	Low	Low	Low	Low	Low	High
Martinez-Taboada et al. 2008 (38)	High	High/unclear	Low/unclear	Low	Low	Low	Low	High
Hoffman et al. 2007 (39)	Low	Low	Low	Low	Low	Low	Low	Low

1.5.1 OBSERVATIONAL STUDIES (TCZ and other bDMARDs)

1.3.2.1 Supplementary Table 38. Evidence retrieved for the use of Tocilizumab and other biologic immunosuppressive drugs (bDMARDs): overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Tocilizumab						
Retrospective						
Régent et al. 2016 (40)	Retrospective, multicentre cohort	4	TCZ in GCA	GCA diagnoses based on ACR criteria/ imaging (PET-CT/CDS) + symptoms of GCA, and active disease with inappropriate dose of GC with unacceptable side effect (n=31) or as add-on therapy (severity of disease n=2); steroid-sparing due to comorbidities (n=1). 20 (59%) pts with previous DMARD (MTX n=18; IFX n=3; n=1 for ADA, anakinra, dapsone, AZA, LEF).	na	Retrospective survey in 2015 amongst 1200 physicians for cases treated with TCZ. 2011-2015.
Evans et al. 2016 (41)	Retrospective case series (n=8 patients) with	3	i.v. TCZ (one case switched to s.c.) in 8 patients with GCA (n=1) or LV-GCA (n=7)	GCA treated with TCZ due to refractory/steroid-dependent	na	nsp

	long-term fu, open label			disease. One case with first-line TCZ.		
Loricera et al. 2015 (42)	Open label, retrospective, multicentre cohort	4	TCZ i.v. in refractory GCA or with AE to GC/previous therapy	GCA diagnosis based on ACR criteria. At TCZ initiation: 16 patients had PMR, 7 had asthenia, 5 had headache, 4 had constitutional symptoms, 2 had jaw claudication, and 2 had visual loss. Previous MTX (n=19), AZA (n=1), and leflunomide (n=1). Moreover, 2 patients had also been treated with other bDMARD (etanercept, infliximab, rituximab, and abatacept). TCZ monotherapy (n=10)/ combined with MTX (n=12).	Malignancy, systemic infections (including HBV and HCV) ruled out.	Diagnosis between 1999-2012
Ustekinumab						
Prospective						
Conway et al. 2016 (43)	Prospective registry, open-label, proof of concept study	4	Steroid-sparing effect of Ustekinumab (UST) for the treatment of refractory GCA	**Refractory GCA** fulfilling ACR criteria	nsp	nsp
GCA + TAK (LVV)						
Tocilizumab						
PROSPECTIVE						
Seitz et al. 2011 (44)	Case series (7 pts), prospective, consecutive pts, single centre	4	Efficacy and safety of i.v. TCZ in LVV	Newly diagnosed (TAB or MRI+) and relapsing/refractory LVV: GCA (n=5), LV-GCA, TAK (n=2). 4/5 GCA fulfilled ACR criteria, 2/2 TAK fulfilled ACR criteria.	Contraindications to TCZ	Dec 2009-Jul 2010
TNF-inhibitors + Tocilizumab						
RETROSPECTIVE						

Vinicki et al. 2017 (45)	Retrospective case series (10 pts), single centre	4	Outcome of patients with GCA/TAK treated with bDMARDs (TNFi or TCZ)	GCA or TAK according to ACR criteria with lack of response to previous therapy and/or ≥2 relapses during GC taper	nsp	nsp

1.3.2.2 Supplementary Table 39. Tocilizumab and other bDMARDs: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Régent et al. 2016 (40)	Efficacy and safety	-Clinical description of improvement of signs/symptoms	Clinical records, retrospective survey	Standard statistics	na
Evans et al. 2016 (41)	Long-term efficacy and safety of TCZ	-Disease activity: ITAS, CDS (one case)	Clinical records	Detailed description of each single case	na
Loricera et al. 2015 (42)	Efficacy and AE	Fever≥38°C, constitutional symptoms: asthenia and/or anorexia, weight loss > 5% normal body weight last 6 months.	Clinical records	Detailed description of each single case	na
Conway et al. 2016 (43)	Steroid-sparing effect of UST in refractory GCA	-Refractory disease: inability to taper GC < 10 mg/day due to symptoms of active GCA with a minimum of 2 relapses -relapse: symptoms of active GCA with or without ↑ APR	Registry data	Standard statistics (Wilcoxon signed-rank test)	na
Seitz et al. 2011 (44)	Efficacy and safety of TCZ in LVV	nsp	Rheumatologist MRA at baseline, every 3 mo	nsp	nsp
Vinicki et al. 2017 (45)	Clinical, serological, imaging outcomes bDMARDs (TNFi and TCZ) in LVV	-Disease activity: **TAK**: Kerr criteria **GCA**: worsening or emergence of ≥2 of: 1) fever or other characteristic of systemic involvement; 2)↑APR; 3) clinical manifestations secondary to large vessel involvement; 4) PMR -remission: no active disease	Clinical records	Standard statistics	nsp

		-sustained remission: remission for 6 mo while receiving GC < 10 mg/day			

1.3.2.3 Supplementary Table 40. Tocilizumab and other bDMARDs: intervention/treatment characteristics

Study ID	Follow-up duration	Patient-years	Overall n. of patients	Intervention	Control	Treatment group	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Régent et al. 2016 (40)	Median 13 mo (range 1-48)	na	34	i.v. TCZ 8 mg/kg/mo	na	GC (mean 26.3 ±13.8 mg/day) + i.v. TCZ 8 mg/kg/mo	6.4±4.5 mo	TCZ stopped in 20 pts after 5.6±2.9 mo	nsp	nsp
Evans et al. 2016 (41)	Average 2 years and 10 mo (range 1-4 years and 4 mo)	na	8	i.v. TCZ 8 mg/kg/month + 1 case switched to s.c. TCZ 162 mg/week	na	GC + TCZ; concomitant LEF (n=1)	Average 2 years and 10 mo (range 1-4 years and 4 mo)	Not standardized	nsp	nsp
Loricera et al. 2015 (42)	Retrospective, median 9 months (IQR 6-19)	nsp	22	i.v.TCZ 8 mg/kg/4 weeks	na	Classical management for GCA (at least GC 40 mg/day), followed by csDMARD and finally bDMARDs → TCZ 8 mg/kg/4 weeks	Median 9 months	Maintenance dose ranged 4-8 mg/kg every 4 or 8 weeks.	na	If latent TB → isoniazid at least 4 weeks before TCZ for at least 9 mo
Conway et al. 2016 (43)	nsp	na	14	s.c. UST 90 mg at weeks 0,4,12 (reduced to 8 weeks in 5 pts)	na	Standard care according to BSR guidelines. GC (prednisolone) → csDMARD /bDMARD (MTX n=1, 83%), AZA n=2	Nsp	nsp	nsp	nsp

						(11%), LEF n=1 (7%), ADA n=1 (7%) → UST 90 mg weeks 0,4 then every 8-12 weeks.				
Seitz et al. 2011 (44)	Mean 8.3 mo	na	7: 5 GCA, (3 TAB+)/ LV-GCA and 2 TAK	i.v. TCZ (8 mg/kg/2 weeks for first month, then every 4 weeks)	na	GC (mean dose 29.5 mg/day) + previous DMARDs (MTX n=3; AZA n=1, IFX n=1) +i.v. TCZ (8 mg/kg/2 weeks for first month, then every 4 weeks). 2 patients as first line.	Mean 8.3 mo	TCZ stopped in 2 GCA after 7 mo while on remission	In two TAK pts stopping TCZ → switch to GC+MTX and GC+MTX+IFX	na
Vinicki et al. 2017 (45)	59.6±27.2 (TAK) vs 37.8±33.8 (GCA)	na	5 TAK 5 GCA= 10 LVV	bDMARDs (IFX n=5; ETA n=1; TCZ n=4)	na	Previous GC → previous csDMARD (**TAK**: MTX n=5; Cyc n=3; MMF n=3 / **GCA**: MTX n=5; AZA n=2; MMF n=2) → bDMARD (**TAK**: IFX n=4, TCZ n=1 + concomitant csDMARD in 4 (MTX or MMF) / **GCA**: TCZ n=3, AZA n=2, MMF n=2 + concomitant csDMARD in 2 (MTX/LEF)	59.6±27.2 (TAK) vs 37.8±33.8 (GCA)	GC tapered if sustained remission	Switch among bDMARDs	na

1.3.2.4 Supplementary Table 41. Tocilizumab and other bDMARDs: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Disease duration at treatment start	Primary outcome	Results in active treatment group	Results in control group	p-value
Régent et al. 2016 (40)	70.5±8.2	27	GCA (TAB+ n= 24), LV-GCA (n=11)	18 mo (range 0-107)	-Clinical improvement of symptoms	28/34	na	na
					-CRP values	40-4±45-6 mg/L baseline → 1.5±1.8 timepoint not specified	na	<0.0001
					-GC taper	26.3±13.8 baseline--± 10.3±8.3 timepoint not specified	na	<0.0001
					-Flare	8/23 (34.8%) after 3.5±1.3 mo of stopping TCZ	na	na
Evans et al. 2016 (41)	nsp (70)	nsp (50%)	GCA and LV-GCA (PET/CT, CDS)	nsp (16 mo)	-ITAS	Reduced to 0 in all cases	na	na
					-CRP values	70.3 mg/L at baseline → 2.5 mg/L last fu	na	na
					-GC dose	24.6 mg/day at baseline→ 4.7 mg/day last fu	na	na
Loricera et al. 2015 (42)	69±8	77%	Cranial (73% TAB+), 15 LV-GCA (PET/MRA/CTA/CT)	14.5 months (5-38)	- Efficacy	-19/22 pts rapid (from month 1) and durable clinical improvement (15 pts asymptomatic at 3 months)	na	na
						-after median fu of 9 months: significant reduction in CRP and ESR	na	<0.0001
						-GC dose reduction: from 18.75 (10-45) to 5 (2.5-10). 4 patients stopped GC.	na	<0.0001
Conway et al. 2016 (43)	69.6±8.6	11 (79%)	GCA (LV-GCA 50%)	29.5 (IQ 12.8-45.5)	-Comparison median GC dose prior to UST and at last fu	20 mg/day (IQR 15, 25) pre-UST → 5 (2.9,8.1) last fu	na	0.001
					-Relapse	0	na	na
					-ESR levels	14 (IQR 5.8,29.3) pre-UST → 15 (9.8,28.5) last fu	na	0.572

					-CRP levels	12.2 mg/L (IQR 3.4,21) → 4.8 (2.8,15)	na	0.177
					-relapse	0 (but dose frequency shortened in 5 due to persistently active disease)	na	na
					-Stopped GC	4 (29%)	na	na
					-Stopped other immunosuppressants	11 (92%)	na	na
Seitz et al. 2011 (44)	GCA: 70 (range 63-79) TAK: 33.5	4	GCA, LV-GCA, TAK	GCA: 1.3 years TAK: 4.9 years	-Complete remission	6/7 within 2 mo	na	na
					-APR normalisation	6/7 after first infusion, 7/7 after 3 mo	na	na
					-imaging changes (MRA)	No changes after 1 mo, improvement after 3 mo in 2/2 TAK, resolved in 1 LV-GCA	na	na
					-GC dose	Reduced in 7/7, stopped in 2	na	na
					-TCZ discontinuation	2/5 GCA after 7 mo without relapse 2/2 TAK after 4 mo (insurance) and 8 mo (relapse).	na	na
Vinicki et al. 2017 (45)	Nsp (TAK 43.4; GCA 81.6)	TAK 5 GCA 4	GCA, TAK	nsp	-remission	100% before 6 mo from bDMARD initiation	ns	ns
					-relapse	1	ns	ns
					-GC dose	Reduced by 70% (79% in TAK, 60% in GCA)	ns	ns

1.3.2.5 Supplementary Table 42. Tocilizumab and other bDMARDs: safety/events

Study ID	Type of AE	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for	Predictors/associated factors
Régent et al. 2016 (40)	-Serious Infections	nsp	2 (TB and fatal sepsis)	na	na	na	na	na	na	na	na
	-Neutropenia	nsp	3 (1 with discontinuation, 1 transient reduction of dose)	na	na	na	na	na	na	na	na

	-severe ↑LFTs	nsp	1 (with discontinuation)	na	na	na	na	na	na	na	na
Evans et al. 2016 (41)	-serious infections	nsp	1	na	na	na	na	na	na	na	na
Loricera et al. 2015 (42)	-Neutropenia	nsp	2 (1 with discontinuation)	na	na	na	na	na	na	na	na
	-Infections (pneumonia, bilateral pneumonia + CMV sepsis)	nsp	2 (2 discontinuations)	na	na	na	na	na	na	na	na
	-Death due to endocarditis-stroke		1	na							
Conway et al. 2016 (43)	-AE	nsp	6	na	na	na	na	na	na	na	na
	-Withdrawal UST	nsp	3	na	na	na	na	na	na	na	na
	-infections	nsp	4	na	na	na	na	na	na	na	na
Seitz et al. 2011 (44)	None (no detailed description)	nsp	0	na	na	na	na	na	na	na	na
Vinicki et al. 2017 (45)	AE	nsp	2	na	na	na	na	na	na	na	na
	infections	nsp	1	na	na	na	na	na	na	na	na
	death	nsp	1 (GCA)	na	na	na	na	na	na	na	na

1.3.2.6 Supplementary Table 43. Tocilizumab and other bDMARDs: risk of bias assessment (Newcastle-ottawa scale for cohort studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two ∗)
Régent et al. 2016 (40)	∗	na	no	∗	na	Self-report	∗	nsp	3
Evans et al. 2016 (41)	no	na	nsp	∗	na	nsp	∗	nsp	2

Loricera et al. 2015 (42)	*	na	no	*	na	nsp	*	nsp	3
Conway et al. 2016 (43)	*	na	*	*	na	Self-report	nsp	nsp	3
Seitz et al. 2011 (44)	*	na	no	*	na	Self-report	*	nsp	3
Vinicki et al. 2017 (45)	*	na	no	nsp	na	Self-report	*	*	3

1.5.2 META-ANALYSIS (bDMARDs)

1.3.3.1 Supplementary Table 44. Evidence retrieved for the use of Tocilizumab and other biologic immunosuppressive drugs (bDMARDs): overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	End of follow-up for analysis	Included studies
bDMARDs– Meta-analysis						
GCA + TAK = LVV						
Osman et al. 2012 (46)	Meta-analysis of RCTs and observations studies	1a	Effectiveness and safety of bDMARDs (RCTs and observational studies) in GCA and TAK	RCT, non-RCT, observational studies (case-control, cohort, case series ≥2 patients on bDMARDs use (TNFi, TCZ, RTX, ABA, UST) in GCA or TAK.	Inception-October 2012	25 studies: -Hoffman et al (IFX for GCA) -Martinez-Taboada et al. (ETA for GCA) -Seror et al. (ADA for GCA) -Osman et al. (anti-TNF TAK) -Nunes et al. (TNF in TAK)

						-Molloy et al. (TNF in TAK) -Mekinian (IFX in TAK) -Kaneko et al. (IFX in 3 adolescent TAK) -Hoyer et al. (RTX in TAK) -Filocamo et al. (TNFi 4 children) -Della Rossa (IFX in 2 TAK) -Comarmond et al. TNFi in TAK) -Cantini et al. (IFX in 4 GCA) -Canas et al. (TCZ in colombian TAK) -Galarza et al. (RTX) -Buonuomo et al. (IFX in 2 TAK) -Beyer et al. (IL-6 in 3 GCA) -Andonopoulos et al. (IFX in 2 GCA) -Schmidt et al. (TNFi in TAK) -Hoffman et al. (TNFi in TAK) -Unizony (design of GIACTA) -Seitz et al. (IL-6 in LVV) -Sciacia et al. (IL6 in 2 GCA) -Salvarani et al. (TCZ in 4 LVV)

1.3.3.2 Supplementary Table 45. Tocilizumab and other bDMARDs: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Osman et al. 2012 (46)	Effectiveness and safety of bDMARDs in LVV	As defined in single trials and studies. Only included studies defining remission as: normalization of clinical symptoms while on GC < 10 mg/day + normalization of APR + absence of new/active changes in fu radiography (RMA, CTA, PET-CT).	Rheumatologist	DerSimonian and Laird random effects model after pooling data from case series. I-squared for heterogeneity.	nsp

1.3.3.3 Supplementary Table 46. Tocilizumab and other bDMARDs: intervention/treatment characteristics

Study ID	Follow-up duration	Overall n. of patients	Active treatment group	n. of patients	Control group	n. of patients	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Osman et al. 2012 (46)	nsp (single studies data)	95 GCA 98 TAK -3 RCTs (n=131) -22 case series (n=150)	bDMARDs -18 studies on TAK: 4 with TCZ, 2 RTX, 12 TNFi -10 studies for GCA: 5 TCZ, 5 TNFi	95 GCA 98 TAK	Placebo (only for RCTs)	nsp (single studies data)	nsp (single studies data)	nsp	nsp	nsp

1.3.3.4 Supplementary Table 47. Tocilizumab and other bDMARDs: population characteristics and control and comparison

Study ID	Age	% females	GCA subtype	Primary outcome	Results in active treatment group	Results in control group	p-value

Osman et al. 2012 (46)	58-85 (GCA) 28-30 (TAK)	73.9% (GCA) 89.7% (TAK)	GCA TAK	1)Establishment of disease remission in GCA or TAK; 2) GC reduction, bDMARDs AE	-TNFi seem not to benefit in GCA -TCZ case series :19 achieved remission -Reduce GC (mean difference -16.55 mg/day (95%CI: -26.24-6.86	nsp (no pooled data)	nsp

1.3.3.5 Supplementary Table 48. Tocilizumab and other bDMARDs: safety/events

Study ID	Type of AE/event/outcome	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	p-value	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for
Osman et al. 2012 (46)	**GCA** -TCZ	11 (36.8%)	11 (36.8%)	na	na	na	na	na	na	na	na
	-IFX	26 (78.9%)	26 (78.9%)	na	na	na	na	na	na	na	na
	-ETA	8 (100%)	8 (100%)	na	na	na	na	na	na	na	na
	-ADA	24 (70.59%)	24 (70.59%)	na	na	na	na	na	na	na	na
	TAK -TCZ	na	na	na	na	na	na	na	na	na	na
	-IFX	23 (27%)	23 (27%)	na	na	na	na	na	na	na	na
	-ETA	3 (25%)	3 (25%)	na	na	na	na	na	na	na	na
	-ADA	nsp	nsp	na	na	na	na	na	na	na	na
	-RTX	nsp	nsp	na	na	na	na	na	na	na	na

1.3.3.6 Supplementary Table 49. Tocilizumab and other bDMARDs: risk of bias assessment (AMSTAR tool)

Study ID	Was a priori design provided?	Duplicate study selection and data extraction?	Comprehensive literature search performed?	Status of publication (grey literature) used as inclusion criteria?	List of studies provided?	Characteristics of the studies provided?	Scientific quality of the included studies assessed and documented?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies appropriate?	Likelihood of publication bias assessed?	Conflict of interest included?

Osman et al. 2012 (46)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

1.6 OTHER TREATMENTS

1.4.1 OBSERVATIONAL STUDIES (other treatments)

1.4.1.1 Supplementary Table 50. Evidence retrieved for other treatments for giant cell arteritis: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Dapsone						
Ly et al. 2016 (47)	Retrospective inception cohort	4	**Steroid sparing** effect and safety of dapsone as adjunctive therapy to GC in GCA	Before 1990: Newly diagnosed GCA TAB+ After 1990: Newly diagnosed GCA ACR criteria/2 ACR criteria (age and ESR) + positive PET Difficult to treat GCA after ≥ 2 flares/relapses, GC toxicity or both	nsp	January 1976-February 2016

1.4.1.2 Supplementary Table 51. Other treatments: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Ly et al. 2016 (47)	Steroid-sparing effect of dapsone and safety	-Relapse: reoccurrence of clinical symptoms and/or inflammatory	Computerized file and clinical records	Standard statistics Mann-whitney, chi squared or Fisher exact	nsp

		parameters attributed to GCA which required increased in treatment. -Prolonged complete remission: ≥ 9 mo remission without GC -Mean monthly decrease in GC dose: divide GC dose before dapsone and after dapsone discontinuation by the duration of dapsone treatment			

1.4.1.3 Supplementary Table 52. Other treatments: intervention/treatment characteristics

Study ID	Follow-up duration	Patient-years	Overall n. of patients	Intervention	Control	Treatment group	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Ly et al. 2016 (47)	87.2±67.5	nsp	72 dapsone + 395 controls	GC + Dapsone -first line (n=18) or -second line after ≥ 2 flares/relapses, GC toxicity or both (n=52)	GC alone (n=395)	GC (PRED) 0.6-1 mg/kg according to clinical severity (often pulses 300 mg-1g for 1-3 days in ischaemic) until symptoms free and CRP < 5 mg/L + Dapsone 50 mg/day (up to 100 mg/day)	10.5±9.8 mo (range 0.5-43)	Taper to 0.35 mg/kg within 4-6 weeks.	MTX/dapsone→ TCZ as third line	nsp

1.4.1.4 Supplementary Table 53. Other treatments: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Disease duration at treatment start	Primary outcome	Results in active treatment group	Results in control group	p-value

Ly et al. 2016 (47)	72.2±7.7	47 (67%)	GCA (TAB+ n=79.7%), LV-GCA	15±12.3 mo (range 3-54)	-Mean GC dose at 12 mo	3.8±6.9	7.4±3.9	0.0002
					-GC withdrawal at 1 year	8 (50%)	2 (0.6%)	<0.0001
					-Complete recovery	17 (94.4%)	195 (4393%)	0.0002

1.4.1.5 Supplementary Table 54. Other treatments: safety/events

Study ID	Type of AE	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for	Predictors/ associated factors
Ly et al. 2016 (47)	-AE	44 (64.7%)	na	na	na	na	na	na	na	na	na
	-Hemolysis	22 (31.4%)	na	na	na	na	na	na	na	na	na
	-Agranulocytosis	2 (2.8%)	na	na	na	na	na	na	na	na	na
	-Rash	9 (13%)	na	na	na	na	na	na	na	na	na
	-Neuropathy	3 (4.3%)	na	na	na	na	na	na	na	na	na
	-Hepatitis	3 (4.3%)	na	na	na	na	na	na	na	na	na
	-Dapsone withdrawn	18 (25.7%)	na	na	na	na	na	na	na	na	na

1.4.1.6 Supplementary Table 55. Other treatments: risk of bias assessment (Newcastle-ottawa scale for cohort studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two ∗)

Ly et al. 2016 (47)	*	*	no	*	*	Self-report	*	*	5

2 SPECIFIC TREATMENTS OF ORGAN COMPLICATIONS/RELAPSING/REFRACTORY DISEASE

2.1 Relapse/flare; visual loss

2.1.1 OSERVATIONAL STUDIES (specific treatments)

2.1.1.1 Supplementary Table 56. Evidence retrieved for specific treatment of organ complications/relapsing/refractory disease for giant cell arteritis: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Relapses/flares						
Prospective						
Kermani et al. 2015 (48)	Prospective, multicenter, longitudinal study	2b	Frequency, timing and clinical features of **relapses** in GCA	Newly diagnosed or established GCA satisfying ACR criteria.	nsp	nsp
Alba et al. 2014 (49)	Prospective, longitudinal study, single centre	4	Effect on outcome of concomitant angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) in GCA	GCA with regular fu and ACEi/ARB treatment	nsp	1995-2007
Retrospective						
Restuccia et al. 2016 (50)	Retrospective, longitudinal study, single centre	4	Frequency and characteristics of **flares** (relapses and recurrences) in GCA	GCA TAB+, at least 4 years fu	nsp	January 1986-December 2007
Labarca et al. 2016 (51)	Retrospective cohort, single centre	4	Frequency, characteristics, treatment and outcome of **relapses** in GCA	All GCA, TAB+ patients ≥ 50 years with at least 6 mo fu.		1998-2013
Visual loss						
Retrospective						
Hayreh et al. 2002 (52)	Retrospective, longitudinal, single centre	4	Incidence and extent of visual improvement with GC in visual loss due to GCA	GCA consecutive, TAB+, acute visual loss treated with GC, fu at least 6 weeks (AION 60%,	nsp	1974-1999

				PION 6%; central retinal artery occlusion (12%), cilioretinal artery occlusion (11%), choroidal ischaemia (1%)		
Chan et al. 2001 (53)	Retrospective longitudinal, two centres	4	**Comparison i.v. or p.o. GC** during the first week of treatment in visual loss at presentation of GCA	GCA consecutive, TAB+ with visual loss: AION 72/73; bilateral n=17 (23%), central retinal artery occlusion n=1	nsp	April 1988-November 1988
Gonzàlez -Gay et al. 1998 (54)	Retrospective, longitudinal, multicentric	4	**Predictors and response to treatment for visual loss and stroke in GCA**	GCA TAB+	TAB negative, incomplete clinical data	January 1975-June 1996

2.1.1.2 Supplementary Table 57. Relapses/complications: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Kermani et al. 2015 (48)	Frequency, timing and clinical features of relapses in GCA	-Relapse: new disease activity after a period of remission, or worsening disease activity during fu.	Treating physician	Kaplan-Meier	nsp
Alba et al. 2014 (49)	Prevalence, timing, predictors and clinical features of relapses and association of relapsing course with ischaemic complications, cumulated GC dose, more prolonged treatment periods, higher GC-related side effects.	-Relapse: reappearance of disease-related symptoms, usually accompanied by elevation APR that required treatment adjustment. -Systemic inflammatory response (SIR): fever > 38C, weight losse ≥ 4 kg, Hb < 11 g/L, ESR ≥85 mm/h. ≥3 items= strong SIR; <3 weak SIR.	Treating physician	Kaplan-Meier	nsp
Restuccia et al. 2016 (50)	Frequency and characteristics of flares	-Positive TAB: transmural inflammation of mononuclear cells +/- giant cells -Flare: reappearance of signs/symptoms of GCA/PMR, resolution after ↑ or reintroduction GC, ESR ≥40 mm/h or CRP ≥ 0.5 mg/day. -Relapse: flares during GC treatment	Clinical records	STROBE criteria to collect data, cox-proportional hazards model, Kaplan-Meier.	nsp

		-Recurrences: flares > 1 mo after GC discontinuation -Long-term remission: no recurrence ≥1 year after GC discontinuation			
Labarca et al. 2016 (51)	Characteristics of relapse, relapse rates, treatment and outcome in GCA	-Relapse: either of the following if improvement after GC dose increase: 1) new onset or reappearance of signs/symptoms of GCA with ↑ APR; 2) new onset or reappearance of signs/symptoms of GCA without APR; 3)isolated increase in APR without signs/symptoms of GCA or other explainable aetiology.	Clinical records	Chi-square, cox models, Kaplan-meier Relapse rate (relapses per unit time: low and high relapse rates) to adjust for different fu times)	nsp
Hayreh et al. 2002 (52)	1)Incidence and extent of visual improvement with high-dose GC in visual loss due to GCA 2)Understand cause of discrepancy between improved visual acuity and not of central field on kinetic perimetry	-visual acuity: Snellen test. 20/15, 20/20, 20/25, 20/30, 20740 20/50, 20/60 20/70, 20/80, 20/100, 20/200, 20/400, counting fingers, hand motion, perception of light, no perception of light -Visual fields: Goldmann perimeter. Criteria for improvement: reproducible increase in size of isopter and decrease in depth and size of central scotoma/Amsler grid result. -Improvement visual acuity: constant ≥ 2 lines of Snellen chart/maintained improvement central visual or + improved visual acuity/ visual improvement ≤ 6 weeks from acute loss	Ophthalmologist	Wilcoxon Rank Sum test, Fisher's exact.	nsp
Chan et al. 2001 (53)	Outcome (visual acuity) and side effects of management with GC in the first week after presentation of GCA	-Visual loss: decrease in visual acuity and/or presence of a relative afferent pupillary defect -Major complication: need to transfer out of ophthalmology unit to medical or surgical unit -Visual acuity: counting fingers, Snellen line above 1/60, hand movements two lines, perception of light three lines, no perception of light four lines	Ophthalmologist	Chi square	nsp
Gonzàlez -Gay et	1) frequency,	- Permanent visual loss: partial or complete loss of sight in one or both eyes.	Ophthalmologist, cerebral CT	Forward stepwise non-conditional logistic regression analysis	nsp

al. 1998 (54)	clinical features, and response to treatment of visual manifestations and cerebrovascular ischemic events,	-cerebrovascular accident: stroke and/or transient ischemic attacks (TIAs).			

2.1.1.3 Supplementary Table 58. Relapses/complications: intervention/treatment characteristics

Study ID	Follow-up duration	Patient-years	Overall n. of patients	Intervention	Control	Treatment group	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Kermani et al. 2015 (48)	21.4 ± 13.9 mo	nsp	128	Standard care: GC (n=118, 94%), → csDMARD: MTX (n=19,15%), AZA (3, 2.4%), Cyc (2, 1.6%), MMF (1, 0.7%)→bD MARD	na	At relapse: GC + MTX (n=13; 22%), TNFi (n=2, 3%), MMF (n=2, 3%)	nsp	nsp	MTX (n=13, 22%); TNFi (n=2, 3%), MMF (n=2,35)	nsp
Alba et al. 2014 (49)	7.8 ± 3.3 years	nsp	106	GC → MTX if ≥ 2 relapses	na	GC (PRED) 1 mg/kg/day (up to 60 mg) for 1 mo. Iv methylprednisolone pulse (1 g/day for 3 days) in <48 h visual loss.	Nsp	PRED tapered by mg/week→ 20 mg/day for 1-2 weeks → tapered to 15 mg/day for 1 mo → 10 mg/day for 3-6 mo → 7.5 mg/day for 3-6 mo→ 5 mg/day for 1	MTX 15 mg/week in ≥2 relapses or GC side effects. PRED increased by 10-15 mg/day above the previous effective	Nsp

								year → taper by 1.25 mg/day every 6 mo	dose. If isolated ↑ APR GC dose held for 1 mo before tapering.	
Restuccia et al. 2016 (50)	80 mo (range 49-125)	nsp	157	GC	na	GC (PRED) 40-60 mg/day. If ischemic manifestations could receive i.v. methylprednisolone (1g/day for 3 consecutive days) + MTX (n=4)	nsp	PRED tapered after one mo by 5 mg/2-4 weeks to 20 mg/day→ by 2.5 mg/2-4 weeks to 10 mg/day → 1 mg/1-2 weeks until discontinuation	GC increased to 10-15 mg above last effective dose. In recurrences 10-15 mg/day was initiated	nsp
Labarca et al. 2016 (51)	Median 5.1 years	nsp	286	GC		GC (mean 50.8±13.1 mg/day (7.7% pulses; 109 pts with ≤ 40 mg/day)	nsp	Treating physician	nsp	ASA 47%, statin 25%
Hayreh et al. 2002 (52)	1.9 (IQR 0.8-5.3)	nsp	84	GC i.v. or p.o.	na	-i.v. dexamethasone sodium phosphate 150 mg every 8 hours for 1-3 days→ 80-120 mg/day PRED p.o. (n=41) -p.o. PRED ≥ 80 mg/day (55-120 mg) (n=43)	nsp	At normalisation and stabilisation of ESR and CRP (at least after 2 weeks)	If ESR/CRP rise (no clinical symptom reliable), increase GC to previous level	nsp
Chan et al. 2001 (53)	1 mo	nsp	73	GC (i.v. vs p.o)	na	-i.v. methylprednisolone 1000 mg/day for 3	nsp	nsp	nsp	nsp

						days or 250 mg/4 times/day, 500 mg/day (n=43) -P.o. prednisolone 50-100 mg/day (median 75 mg/day) (n=30)				
Gonzàlez-Gay et al. 1998 (54)	nsp	nsp	239	GC	na	GC 45-80 mg p.o./1 g for 3 days (n=3)	nsp	nsp	nsp	nsp

2.1.1.4 Supplementary Table 59. Relapses/complications: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Disease duration at treatment start	Primary outcome	Results in active treatment group	Results in control group	p-value
Kermani et al. 2015 (48)	69.9±8.6	102 (80%)	GCA (TAB+ 78%) LV-GCA (47%)	4.6 mo (IQR 1.2; 16.8)	-Frequency of relapses	59 in 44 pts (34%)	na	na
					-clinical manifestations of relapse	Headache (42%), PMR (51%), visual manifestations (5%), constitutional (14%)		
					-Treatment at time of relapse	-73% of relapses during GC (median dose 7.5 mg/day, range 0-35) -54% at GC dose 1-10 mg/day -17% at GC dose 11-20 mg/day -5% at GC dose > 20 mg/day -17% at GC discontinuation	na	na
Alba et al. 2014 (49)	75±7 (range 58-89)	77	GCA (TAB+)	16±21 weeks	-Frequency of relapse	64% at least 1 relapse 36% ≥ 2 relapses 50% during first year of disease	na	na

					-Clinical manifestations of relapse	PMR (51%), cranial (31%), constitutional (18%). 1 visual loss	na	na
					-predictors of relapse	PMR, scalp tenderness, higher intensity of systemic inflammatory response	na	na
					-treatment at time of relapse	5.3±6.5 mg/day 50% GC ≤ 2.5 mg/day	na	na
					-Time to GC dose < 10 mg/day (relapsing vs non-relapsing)	40 weeks vs 27	na	<0.0001
					-Time to GC dose < 5 mg/day (relapsing vs non-relapsing)	16.3 weeks vs 89.5	na	0.004
					-Time to GC discontinuation (relapsing vs non-relapsing)	340 weeks vs 190	na	<0.001
					-Cumulative GC dose first year (relapsing vs non-relapsing)	6.2±1.7 g vs 5.4±0.78 g	na	0.015
Restuccia et al. 2016 (50)	74±7.9	123 (78%)	GCA (TAB+)	nsp	-Frequency of flares	≥ 1 flare in 36.5% 46.4% first 2 years of disease	na	na
					-Treatment at time of flare	GC ≤10 mg/day (82.9%)	na	na
					-Clinical manifestations of flare	PMR (46.5%), cranial (41.9%)	na	na
					-Cumulative GC first year (flaring vs non-flaring)	7.8±2.4 g vs 6.7±2.4	na	0.02
					-Total cumulative GC (flaring vs non-flaring)	15.5±8.9 g vs 10±9.2	na	0.0001
					-Duration of GC (flaring vs non-flaring)	58±44 mo vs 30±39	na	0.0001

					-Predictors flares	Baseline systemic symptom's (p=0.02), ↓ Hb (p=0.05), fever (p=0.02), giant cells TAB (p=0.04), intraluminal acute thrombosis TAB (p=0.007), moderate/severe inflammatory infiltrate TAB (p=0.009)	na	na
					-Predictive model of flares	Fever HR 2.14 (95%CI 1.06-4.32)	na	0.03
						TAB infiltrate severity HR 5.41 (95%CI 1.64-17.87)	na	0.006
Labarca et al. 2016 (51)	75±7.6	213 (74%)	GCA (TAB+)	2.1 mo (IQR 0.9-4.4)	-Frequency of relapse	80 pts 1 relapse 133 pts ≥2 relapses 50% during first year of disease 68% by second year 79% by 5 years	na	na
					-Clinical characteristics	PMR (33%), headache (32.3%), malaise/fatigue (20.6%), scalp tenderness (7.8%)	na	na
					-Predictors of relapse	Established hypertension and diabetes, female. History of venous thrombosis and leg claudication earlier relapse	na	na
					-Correlation initial GC dose (> 40 mg/day vs ≤ 40 mg/day) and probability to reach dose < 5 mg/day sooner	HR 1.46; (95% CI 1.09,1.96)	na	na
					-Correlation initial GC dose (> 40 mg/day vs ≤ 40 mg/day) and probability to discontinue GC sooner	HR 1.56; (95% CI 1.09,2.23)	na	na

Hayreh et al. 2002 (52)	76.6±7.4	61 (73%)	GCA visual loss, TAB+	1.9 years (IQR 9.6 mo-5.3 years)	-Improved visual acuity (≥ 2 lines) and central visual filed (i.v. vs p.o.)	5 (4%) eyes in 5 pts: 3 vs 2	na	na
					-Improved visual acuity alone	7 eyes in 6 pts	na	na
					-Visual improvement (i.v. vs p.o.)	7% vs 5%	na	0.672
					-Visual improvement both visual acuity and fields	Shorter interval between onset and GC initiation	na	0.065
Chan et al. 2001 (53)	Mean 75	2:1	GCA visual loss, TAB+	First 7 days	-Vision improvement (i.v. vs p.o.)	21 (29%) overall: 17 (23%) vs 4 (5%)	na	0.01
					-Snellen lines improvement	2.3 vs 1.5	na	0.85
					-No vision improvement	43 (59%) overall: 19 (26%) vs 24 (33%)	na	nsp
					-Vision worse	9 (12%) overall: 7 (10%) vs 2 (35)	na	0.22
					-Visual outcome (higher GC > 15 mg/kg/day vs lower GC ≤ 15 mg/kg/day)	-improved: 6 vs 10 -Same: 6 vs 13 -Worse: 4 vs 4	na	0.66
Gonzàlez-Gay et al. 1998 (54)	73.6±6.8 (ocular symptoms); 73.4±6.6 (no ocular)	38 (55.1%) vs 95 (55.9%)	GCA	1.2-2 mo	-Improvement visual loss	(n=8) OR 22.4 (95%CI 1.9-1070.1) with treatment < 24 hours	na	na

2.1.1.5 Supplementary Table 60. Relapses/complications: safety/events

Study ID	Type of AE	N/% of events	N cases in treatment group	N cases in contr	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for	Predictors/associated factors

				ol group							
Kermani et al. 2015 (48)	Not assessed	na	na	na	na	na	na	na	na	na	na
Alba et al. 2014 (49)	-Osteoporosis (relapsing vs non-relapsing)	65% vs 32%	na	na	na	na	na	na	na	na	P=0.001
	-Diabetes	10% vs 5%	na	na	na	na	na	na	na	na	nsp
	Hypertension	54% vs 45%	na	na	na	na	na	na	na	na	nsp
	Hypercholesterolemia	62% vs 69%	na	na	na	na	na	na	na	na	nsp
	Cushing	12% vs 3%	na	na	na	na	na	na	na	na	nsp
	Cataracts	23.5% vs 8%	na	na	na	na	na	na	na	na	nsp
Restuccia et al. 2016 (50)	Not assessed	na	na	na	na	na	na	na	na	na	na
Labarca et al. 2016 (51)	-AE	29% during first year, 46% by 2 years, 73% by 10 years	na	na	na	HR	1.18 (95%CI 0.83,1.67)	na	na	na	P= 0.36 (between initial GC dose > 40 mg/day vs ≤ 40 mg/day)
	-Osteoporosis	25% rate by 10 years (27% fractures)	na	na	na	na	na	na	na	na	na
	-Hypercortisolism	16%	na	na	na	na	na	na	na	na	na
	-Serious infections	17%	na	na	na	na	na	na	na	na	na
	-New hypertension	1.7% (rate by 10 years)	na	na	na	na	na	na	na	na	na
	-Dyslipidaemia	2%	na	na	na	na	na	na	na	na	na
	-Avascular necrosis	2.3%	na	na	na	na	na	na	na	na	na
	-Heart failure	6.8%	na	na	na	na	na	na	na	na	na
	-Death	32% (10-year mortality rate)	na	na	na	HR	0.99 (95%CI 0.83,1.19)	na	na	na	P=0.94 (effect of total number of relapses on mortality)
Hayreh et al. 2002 (52)	Not assessed by study	na	na	na	na	na	na	na	na	na	na

Chan et al. 2001 (53)	-Major complications (angina, pulmonary oedema, haematoma, hypertension)	4 (9.3%) i.v. group	na	na	na	na	na	na	na	na	na
Gonzàlez-Gay et al. 1998 (54)	Not assessed by study	na	na	na	na	na	na	na	na	na	na

2.1.1.6 Supplementary Table 61. Relapses/complications: risk of bias assessment (Newcastle-ottawa scale for cohort studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two *)
Kermani et al. 2015 (48)	*	na	*	*	na	Self-report	*	*	5
Alba et al. 2014 (49)	*	na	no	*	na	Self-report	*	nsp	3
Restuccia et al. 2016 (50)	*	na	no	*	na	Self-report	*	nsp	3
Labarca et al. 2016 (51)	*	*	no	*	na	Self-report	*	nsp	4
Hayreh et al. 2002 (52)	*	*	no	*	na	Self-report	*	nsp	4
Chan et al. 2001 (53)	*	*	no	*	na	Self-report	*	nsp	4
Gonzàlez-Gay et al. 1998 (54)	*	*	no	nsp	na	Self-report	nsp	nsp	2

3 SPECIFIC DISEASE GROUPS: LVV

3.1 Large vessel GCA

3.1.1 OBSERVATIONAL STUDIES (specific disease groups)

3.1.1.1 Supplementary Table 62. Evidence retrieved for specific disease groups in giant cell arteritis: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
LV-GCA						
De Boysson et al. (55)	Retrospective, longitudinal, multicenter	4	Is LV-GCA treated differently than cranial GCA? comparison of **LV-GCA (PET+) vs GCA (PET neg)**	Newly diagnosed GCA, satisfying ACR criteria or 2 criteria + LV-GCA on imaging + available PET-CT result ≤ 5 days from GC initiation + FU ≥ 12 mo	nsp	2005-2015
Czihal et al. 2015 (56)	Retrospective longitudinal single centre	4	Impact of extent of vascular involvement by CDS on treatment response	Newly diagnosed GCA fulfilling ACR criteria or TAB+, or CDS+ together with typical clinical signs and inflammatory response, rapidly responsive to GC	nsp	2002-2010
Czihal et al. 2013 (57)	Retrospective cross-sectional, single centre	4	Long-term outcome of LV-GCA of the arms treated with medical treatment alone	Newly diagnosed LV-GCA of proximal arms (subcl, AX, proximal brachial arteries) with CDS at baseline and at 6 mo	nsp	January 2002-December 2010

3.1.1.2 Supplementary Table 63. Specific disease groups: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
De Boysson et al. (55)	Differences in initial treatment and outcome between GCA (PET neg) and LV-GCA (PET+)	-Positive PET-CT: circumferential smooth-line FDG vascular uptake > that of liver (Meller) in at least 1 of 8 segment: thoracic aorta, abdominal aorta, subclavian, axillary, carotid, iliac/femoral, upper or lower limb arteries. -Steroid dependent: PRED > 20 mg/day at 6 mo or > 10 mg/day at 12 mo -Relapse: reoccurrence of symptoms or lab findings requiring increase in GC or GC-sparing agent	Standardized form	Standard statistics	nsp
Czihal et al. 2015 (56)	Relapse rate, taper of GC < 10 mg/day, need for steroid-sparing agents	-Relapse: recurrence of clinical signs/symptoms or rise in APR with improvement after ↑ GC dose	Clinical records	Standard statistics (Kaplan-Meier for relapses)	nsp
Czihal et al. 2013 (57)	Clinical, haemodynamic and sonographic follow-up of LV-GCA of proximal arm arteries	-Arm claudication: intermittent muscle pain or weakness of upper extremities during arm exercise disappearing after short rest	Clinical records CDS	Standard statistics (Fisher's, Mann-Whitney)	nsp

3.1.1.3 Supplementary Table 64. Specific disease groups: intervention

Study ID	Follow-up duration	Patient-years	Overall n. of patients	Intervention	Control	Treatment group	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
De Boysson et al. (55)	Median 56 mo	nsp	80	GC 0.75 mg/kg	na	GC 0.75 mg/day	na	nsp	Increase in GC dose or GC-sparing agent: MTX n=12; Disulone n=5; AZA n=1, Cyc	nsp

									n=2, TCZ n=2, IFX n=1	
Czihal et al. 2015 (56)	25.4 mo	nsp	43 -AX/subcl (n=17) -AX/subcl + TA (n=9) -TA (n=17)	Standard care GC→ csDMARD or bDMARDs	na	GC 40-60 mg/day until symptoms and lab resolution	nsp	Taper by 10 mg/2 weeks → 20 mg/day, then by 2.5 mg/2 weeks → 10 mg/day, then by approximately 1 mg/4 weeks	GC-sparing agents MTX n=13; AZA n=3; Cyc n=2, ADA n=2; IFX n=2, MMF n=1; ETA n=1; RTX n=1	nsp
Czihal et al. 2013 (57)	21.9±17.1 mo (range 6-88)	nsp	34 (47.1% with arm claudication)	Standard care (EULAR recommendations) GC → csDMARD /bDMARD	na	GC at follow up 7.5 mg±8 mg (range 0-40)	nsp	nsp	csDMARD or b/DMARD: MTX n=7, ADA n=2, AZA n=1, Cyc n=1)	ASA

3.1.1.4 Supplementary Table 65. Specific disease groups: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Disease duration at treatment start	Primary outcome	Results in active treatment group	Results in control group	p-value
De Boysson et al. (55)	71 (range 53-87)	50	GCA (PET neg) LV-GCA (PET+)	nsp	-Initial GC dose (LV-GCA vs GCA)	0.74 mg/kg vs 0.75 mg/kg	na	0.56
					-GC dose 12 mo (LV-GCA vs GCA)	0.07 mg/kg vs 0.06 mg/kg	na	0.23
					-GC discontinuation last fu (LV-GCA vs GCA)	22 (55%) vs 20 (50%)	na	0.65
					-GC-sparing agents (LV-GCA vs GCA)	12 vs 10	na	ns
Czihal et al. 2015 (56)	66.1±7.7 (LV-GCA) vs 72.1±6.6	81% vs 65%	GCA (CDS+) LV-GCA (CDS+)	nsp	-Time to GC < 10 mg/day (LV-GCA vs cranial GCA)	29.2±10.8 weeks (LV-GCA) vs 40.5±32.9 (cranial GCA)	na	0.12

	(cranial GCA)							
					-Need for GC-sparing agents	-LV-GCA vs cranial-GCA Details in figure - AX/subcl +TA GCA vs AX/subcl GCA vs TA GCA	na na	0.34 0.04
Czihal et al. 2013 (57)	66.2±6.5	28 (82.4%)	LV-GCA proximal arm arteries	nsp	-Complete resolution of CDS wall thickening at mean 21 mo	32.4%	na	na
					-New ischaemic symptoms	0	na	na
					-Resolution of symptoms	5	na	na

3.1.1.5 Supplementary Table 66. Specific disease groups: safety/events

Study ID	Type of AE	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for	P value-Predictors/associated factors
De Boysson et al. (55)	-Death (LV-GCA vs GCA)	1 (3%) vs 7 (18%)	na	na	na	na	na	na	na	na	P=0.06
Czihal et al. 2015 (56)	-AE (infections, OP, hypertension, diabetes, dyslipidemia)		na	na	na	na	na	na	na	na	ns
Czihal et al. 2013 (57)	-Hypertension	22 (64.7%)	na	na	na	na	na	na	na	na	ns
	-Diabetes	7 (20.6%)	na	na	na	na	na	na	na	na	ns

3.1.1.6 Supplementary Table 67. Specific disease groups: risk of bias assessment (Newcastle-ottawa scale for cohort studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two ∗)

				present at start of study			outcomes to occur		
De Boysson et al. (55)	*	na	no	*	na	Self-report	*	nsp	3
Czihal et al. 2015 (56)	*	na	no	*	na	Self-report	*	nsp	3
Czihal et al. 2013 (57)	*	na	nsp	*	na	nsp	*	nsp	3

4 REVASCULARISATION PROCEDURES

4.1. Vessel stenosis/aneurysms

4.1.1 OBSERVATIONAL STUDIES (surgery)

4.1.1.1 Supplementary Table 68. Evidence retrieved for surgical/revascularisation procedures in giant cell arteritis: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Management of vessel stenosis						
Retrospective						
Both et al. 2006 (58)	Retrospective, single centre	4	Outcome of PTA of upper extremities stenosis in GCA	GCA all but one patient satisfying ACR criteria	Stenosis of other vessels other than subclavian, axillary, brachial	1995-2004
Management of vessel aneurysms						
Retrospective						
Gagné-lorenger et al. 2016 (59)	Retrospective cohort, single centre	4	Clinical characteristics and outcome of surgical management of thoracic aorta involvement (aneurysm+/-dissection) in GCA	GCA with pathologic evidence on operated aorta	nsp	nsp
Zehr et al. 2005 (60)	Retrospective cohort, single centre	4	Results of surgical treatment of ascending aortic aneurysms in GCA	GCA with ascending aortic aneurysm	nsp	January 1995-December 2002
LVV						
Management of vessel stenosis						
Retrospective						
Both et al. 2003 (61)	Retrospective, single centre	4	Safety and effectiveness of PTA of occlusive arterial disease in LVV	TAK and GCA according to ACR criteria	nsp	January 1994-May 2000

4.1.1.2 Supplementary Table 69. Surgery: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Both et al. 2006 (58)	Outcome of balloon angioplasty in the arteries of the upper extremities in GCA	-Indication: ischaemic symptoms persisting despite immunosuppressive treatment. - Primary patency: uninterrupted patency of the treated lesion, with no repeated procedure during follow-up. -Secondary and tertiary patency: recurrent severe 107stenosis or occlusions revascularised by PTA. -Technically successful: residual stenosis < 30% or the arterial lumen was ≥ 50% larger than before treatment	Medical records, MRA, CDS	Kaplan-Meier	nsp
Gagné-lorenger et al. 2016 (59)	Clinical characteristics and outcome of thoracic aorta involvement (aneurysms+/-dissection) in GCA	nsp	Pathology report, CT/PET	Kaplan-Meier	nsp
Zehr et al. 2005 (60)	Outcome of surgical repair of ascending aorta aneurysms in GCA	-Indications: aortic diameter >5.5 cm or symptomatic aortic regurgitation.	Surgical database, medical records, phone calls	Kaplan-Meier	nsp
Both et al. 2003 (61)	Safety and effectiveness of PTA of occlusive arterial disease in LVV	-Technically successful: residual stenosis <30% or the arterial lumen ≥50% compared with the status before treatment.	Medical records	nsp	nsp

4.1.1.3 Supplementary Table 70. Surgery: intervention

Study ID	Follow-up duration	Patient-years	Overall n. of patients	Intervention	Control	Treatment group	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Both et al. 2006 (58)	24 mo	nsp	30	PTA + GC + csDMARD	na	PTA + GC + MTX (n=8) +/- Cyc (800-1000 i.v. every 15-21 days)	nsp	nsp	Reintervention	After intervention, i.v. 24 000 IU heparin for 24 h to increase partial thromboplastin time (60–80 s). ASA 100 mg/day (n=8) clopidogrel 75 mg/day (n=2).
Gagné-lorenger et al. 2016 (59)	4.2±2.3 years	nsp	40	Surgery thoracic aorta	na	Total thoracic aorta replacement (n=4), arch replacement (n=34, 85%), aortic valve procedure (n=32, 80%)	nsp	nsp	nsp	nsp
Zehr et al. 2005 (60)	2.8±2.3 years	nsp	37	Open surgery thoracic aorta	na	Surgery (ascending aorta replacement +/- valve replacement)	nsp	nsp	nsp	nsp
Both et al. 2003 (61)	12 mo	nsp	11	PTA +/- stent	na	PTA +/- stent +/- csDMARD (AZA, MTX)	nsp	nsp	nsp	ASA or clopidogrel long-term

4.1.1.4 Supplementary Table 71. Surgery: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Disease duration at	Primary outcome	Results in active treatment group	Results in control group	p-value

				treatment start				
Both et al. 2006 (58)	Single cases	nsp	LV-GCA with upper extremities involvement	nsp	-Technical success	100%	na	nsp
					-Primary patency	62.5%	na	nsp
					-Secondary patency	82.6%	na	nsp
					-Tertiary patency	82.6%	na	nsp
Gagné-lorenger et al. 2016 (59)	66.6±9.1	22 (55%)	LV-GCA thoracic aorta involvement	nsp	Outcome/safety surgery	na	na	na
Zehr et al. 2005 (60)	69.6±9.5	29 (78.4%)	LV-GCA ascending aorta involvement	nsp	-Safety/outcome	na	na	na
Both et al. 2003 (61)	35-82	10	TAK or GCA (TAB+ n=2)	nsp	-Technical success	25/25 (100%)	nsp	nsp

4.1.1.5 Supplementary Table 72. Surgery: safety/events

Study ID	Type of AE/event	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for	Predictors/associated factors
Both et al. 2006 (58)	-Complications	3 (pseudoaneurysm, moderate vessel wall dissection, haematoma)	na	na	na	na	na	na	na	na	na
	-Recurrences	5	na	na	na	na	na	na	na	na	na
Gagné-lorenger et al. 2016 (59)	-Perioperative complications	Stroke (1), seizure (4), infection (1), atrial fibrillation (16),	na	na	na	na	na	na	na	na	na

		pneumonia (8), low cardiac output (1), bleeding (3)									
	-reinterventions	4	na	na	na	na	na	na	na	na	na
	-Mortality	Hospital (0)	na	na	na	na	na	na	na	na	na
	-5-year survival	91%	na	na	na	na	na	na	na	na	na
Zehr et al. 2005 (60)	-Reexploration for bleeding	3 (8%)	na	na	na	na	na	na	na	na	na
	-Stroke	3 (8%)	na	na	na	na	na	na	na	na	na
	-Prolonged ventilator support (>24 h)	8 (21.6%)	na	na	na	na	na	na	na	na	na
	-Atrial fibrillation	12 (32.4%)	na	na	na	na	na	na	na	na	na
	-Early mortality	0	na	na	na	na	na	na	na	na	na
	-Late mortality	8	na	na	na	na	na	na	na	na	na
Both et al. 2003 (61)	-Restenosis	9	na	na	na	na	na	na	na	na	na
	-Dissection	3	na	na	na	na	na	na	na	na	na
	-Arterial rupture	1	na	na	na	na	na	na	na	na	na

4.1.1.6 Supplementary Table 73. Surgery: risk of bias assessment Newcastle-ottawa scale for cohort studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two ∗)

Both et al. 2006 (58)	*	na	nsp	*	na	nsp	*	nsp	3
Gagné-lorenger et al. 2016 (59)	*	na	*	*	na	nsp	*	nsp	4
Zehr et al. 2005 (60)	*	na	*	*	na	na	*	nsp	4
Both et al. 2003 (61)	no	na	no	*	na	nsp	*	nsp	2

5 ADJUNCTIVE THERAPIES AND PROHYLAXIS

ASPIRIN

Other issues related to cardiovascular/cerebrovascular disease

Infections prophylaxis (PJP), vaccinations

5.1 Aspirin/cardiovascular

5.1.1 OBESERVATIONAL STUDIES (ASA/cardiovascular)

5.1.1.1 Supplementary Table 74. Evidence retrieved for adjunctive therapy and prophylaxis in giant cell arteritis: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Aspirin/Anti-platelet agents						
Retrospective						
Salvarani et al. 2009 (62)	Retrospective population-based incident cohort	4	Impact of traditional CV risk factors, carotid atherosclerosis assessed by ultrasonography, past history of ischaemic CV events, and the effect of anti-platelet or anti-coagulant therapy on the	GCA TAB+	nsp	1986-2005

			occurrence of severe cranial ischaemic events			
Berger et al. 2009 (63)	Retrospective longitudinal cohort	4	How platelet count, size and inhibition (ASA) relate to ischaemic complications in GCA	Newly diagnosed GCA ≥ 3 ACR criteria, or < 3 ACR criteria + TAB + evidence of GCA (AION or PET)	Missing data for classification, negative TAB, < 3 ACR criteria	June 1997-June 2007 (TAB) and January 2003-January 2007 (Inpatients charts)
Narváez et al. 2008 (64)	Retrospective follow-up of unselected patients	4	Whether concomitant ASA or antiplatelets have impact on severe ischemic complications and outcome of GCA	GCA satisfying ACR criteria (TAB+ or ≥ 4 criteria and response to GC)	nsp	January 1986-December 2004
Lee et al. 2006 (65)	Retrospective longitudinal cohort	4	Whether antiplatelet or anticoagulation reduces ischaemic events in GCA	GCA satisfying ACR criteria	nsp	January 1989-November 2004
Nesher et al. 2004 (66)	Retrospective longitudinal cohort	4	Effect of ASA before GCA diagnosis and after GC therapy on cranial ischaemic events	GCA TAB+ or ACR criteria	Fu < 3 mo	1980-2000
Gonzalez-Gay et al. 2004 (67)	Retrospective longitudinal cohort	4	Effect of traditional risk factors of atherosclerosis (and anti-platelet/anticoagulants) in the development of severe ischaemic complications in GCA	GCA TAB+	nsp	January 1981-December 2001
Statins						
Prospective						
Pugnet et al. 2016 (68)	Population-based incident cases cohort	2b	Effect of statin exposure on cardiovascular hospitalization in newly diagnosed GCA	Incident newly diagnosed GCA: Age ≥ 50 years, ICD code for GCA, at least one prescription GC with diagnosis validated by the French National Health Insurance system physician	nsp	January 2005-April 2011
Pugnet et al. 2015 (69)	Population-based incident cases cohort	2b	Role of statins on occurrence of GCA and GC requirements in newly diagnosed GCA	Incident newly diagnosed GCA: Age ≥ 50 years, ICD code for GCA, at least one prescription GC with diagnosis validated by the French National Health Insurance system physician → continuous GC use (at least 4	nsp	January 2005-December 2008 → follow up until April 2011

				prescriptions) during 6 mo, no GC < 6 mo prior.		
Retrospective						
Narváez et al. 2007 (70)	Retrospective fu cohort, single centre	3b	If concomitant treatment with statins has impact on ischaemic complications, relapses, late complications (aortitis), recovery and GC requirements in GCA	GCA satisfying ACR criteria, TAB+ or 4 ACR criteria and response to GC	nsp	January 1986-December 2004
GarcÍa-martÍnez et al. 2004 (71)	Retrospective, longitudinal, single centre	3b	If concomitant treatment with statins has impact on outcome: GC requirements, relapses, disease activity.	GCA TAB+ with statins at diagnosis or during first year GC therapy, or not exposed to statins	nsp	1997-2004
Angiotensin II receptor blockers						
Prospective						
Alba et al. 2014 (72)	Prospective cohort, single centre	3b	If concomitant treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) influences outcome in GCA	GCA TAB+, regular fu for at least 4 years	nsp	1995-2007

5.1.1.2 Supplementary Table 75. Adjunctive therapy/prophylaxis: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Salvarani et al. 2009 (62)	Impact of traditional CV risk factors and anti-aggregants/anticoagulant therapy on severe cranial ischaemic events	Cranial ischaemic events: visual loss and cardiovascular accidents were considered and attributed to GCA if they occurred within the time between the onset of GCA symptoms/signs and 1 month after the onset of corticosteroid therapy	Computerized pathology laboratory register; medical records	Multiple logistic regression	nsp
Berger et al. 2009 (63)	How platelet count and size, and ASA relate to ischaemic events in newly diagnosed GCA	-Ischaemic events: jaw claudication, amaurosis fugax, blurred vision in correlation to diagnosis of GCA, -Severe ischaemic events: AION, ischaemic stroke within 2 weeks of diagnosis -Platelet volume: mean platelet volume	Clinical charts	Multiple imputation of missing covariates for multiple logistic regression analysis	nsp

Narváez et al. 2008 (64)	Whether concomitant use of low-dose ASA or other antiplatelet agents had impact on severe ischemic complications and in the outcome of GCA (relapses, recovered, GC requirements).	-Severe ischaemic: visual manifestations (amaurosis fugax, permanent visual loss or diplopia), or cerebrovascular accidents (stroke and/or TIA), limb claudication of recent onset, acute myocardial infarction or unstable angina) from diagnosis within 4 weeks after GC initiation -Relapse: increase or recurrence of GCA symptoms with increase APR during GC taper or during first mo after GC discontinuation + regression of symptoms at increase or resume of GC -Long-lasting GC discontinuation: date of permanent discontinuation without recurrence ≥ 1 year	Clinical charts	Standard statistics, multivariate logistic regression analysis for risk factors of ischaemic events	nsp
Lee et al. 2006 (65)	1)Whether antiplatelet therapy or warfarin affect rate of ischaemic events 2)Bleeding complications	-GCA-related events: if other signs/ symptoms/lab evidence of recurrence. -GCA-related vision loss: retinal artery occlusion or ischemic optic neuropathy. -Bleeding complications: gastrointestinal hemorrhage/ulcer or intracranial bleeding.	Clinical charts	Standard statistics. Forward-adding method of variable inclusion, retaining variables with p value < 0.15 to identify independent risk factors for ischaemic events.	nsp
Nesher et al. 2004 (66)	Effect of ASA on rate of cranial ischaemic events	-GCA-related ischaemic events: at diagnosis or within 14 days or at GC taper/discontinuation if accompanied by GCA signs/symptoms	Clinical records	Standard statistics	nsp
Gonzalez-Gay et al. 2004 (67)	Effect of traditional risk factors of atherosclerosis on ischaemic events	-Severe ischaemic events: visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia), cerebrovascular accidents (stroke and/or transient ischemic attacks), and jaw claudication, limb claudication of recent onset. Attributed to GCA within 4 weeks of GC therapy.	Clinical records	Standard statistics (logistic regression)	nsp
Pugnet et al. 2016 (68)	Effect of statins on cardiovascular-related hospitalization in	-Cardiovascular (CVD) diseases: stroke, coronary artery disease, heart failure, peripheral artery disease, cardiac arrhythmias, hypertension, others (valvular, congenital cardiopathies)	French National Health Insurance system	Kaplan-Meier, Cox regression	Pts with one type of CVD hospitalization were censored for other types

	newly diagnosed GCA				
Pugnet et al. 2015 (69)	Association between statin exposure and GCA occurrence and influence of statin exposure on PRED requirements after GCA diagnosis	-Time to maintenance GC dose: < 5 mg/day with no increase during 6 consecutive mo	French National Health Insurance system	Kaplan-Meier, cox regression	Censored at date of getting first maintenance with low prednisone dose, at death or at date of last drug prescription + 30 days
Narváez et al. 2007 (70)	Effect of concomitant statins on risk of severe ischaemic complications, outcome of GCA, relapses, late complications (aortitis), remission and GC requirements	-Severe ischaemic complications: visual manifestations (transient visual loss, permanent visual loss or diplopia), stroke and TIA, jaw claudication, large-artery stenosis of extremities with limb claudication, ischaemic heart disease. -Ischaemic complications due to GCA: if occurred within onset and 4 weeks after GC therapy -aortitis: signs of dissection, vascular inflammation or luminal changes at MRI, CT or angiography -Relapse: increase or recurrence of GCA symptoms with APR during the reduction of GC dose or during first mo after GC discontinuation with regression of symptoms with increase or resume of therapy -Long lasting remission: permanent discontinuation treatment for ≥ 1 year	Clinical records	Standard statistics (chi squared)	nsp
García-martínez et al. 2004 (71)	Effect of statins on outcome, GC requirements, relapses, disease activity markers	-Time (weeks) to PRED maintenance dose < 10 mg/day without relapse ≥ 3 mo - cumulative GC dose -ESR, CRP	Clinical records	Standard statistics (Kaplan-Meier)	nsp
Alba et al. 2014 (72)	-Time to first relapse -Number of flares -Time to achieve stable GC dose < 10 mg/day and < 5 mg/day with no relapses -Time to discontinue GC	-Relapse: reappearance of disease-related symptoms (cranial, PMR, fever, anemia) resolving by increase GC by 10-15 mg/day above previous dose	Physician	Standard statistics (Kaplan-Meier, Cox-regression models: adjusted for sex, age at diagnosis, co-therapy with ASA, MTX, statins and methylprednisolone pulses)	nsp

	-Cumulative GC dose first year -APR				

5.1.1.3 Supplementary Table 76. Adjunctive therapy/prophylaxis: intervention/treatment characteristics

Study ID	Follow-up duration	Patient-years	Overall n. of patients	Intervention	Control	Treatment group	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Salvarani et al. 2009 (62)	nsp	nsp	180	Anti-platelet/anticoagulant in 10/37 (27%) with ischaemic events	In 16/149 (11.6%)	PRED 40-60 mg/day (some with ocular GC 1 g for 3 days)	nsp	nsp	nsp	nsp
Berger et al. 2009 (63)	Nsp (2 weeks)	nsp	85	N= 22 (26%) ASA	na	ASA at time of diagnosis	nsp	nsp	nsp	nsp
Narváez et al. 2008 (64)	Mean 3.6 years (range 1.1-15.1)	nsp	121	N=37 GC + ASA or anti-platelet agent	N=84 Not receiving anti-platelet agents	GC (40-60 mg/day or 1 g/day for 3 days if visual manifestations) + ASA (100-300 mg/day) n=30; ticlopidine (250 mg/day) n=3; clopidogrel (75 mg/day) n=4	32.6±23.8 vs 36.4±24.3 mo	GC tapered after resolution of reversible symptoms and normalisation APR (usually after 2-4 weeks) then according to physicians' judgement	nsp	nsp
Lee et al. 2006 (65)	4 years	nsp	143	N=86 (60.1%) ASA or anticoagulant → 68 considered as others started	N=57 (39.9%) not receiving antiplatelet agents or anticoagulants	ASA, clopidogrel or warfarin	nsp	nsp	nsp	nsp

				after ischaemic event						
Nesher et al. 2004 (66)	26.4 mo (at least 3 mo)	nsp	36 + 139 (at diagnosis); 73 + 93 (with fu)	N= 73 ASA + GC (36% before GCA)	N=93 not receiving ASA (only GC)	ASA 100 mg/day + GC 40-80 mg/day	nsp	nsp	nsp	nsp
Gonzalez-Gay et al. 2004 (67)	nsp	nsp	210 (n=15 with anti-aggregants /anticoagulant)	GC + anti-aggregants/anticoagulant	GC 40-60 mg/day	GC 40-60 mg/day + ASA 100-250/trifusal 300 mg/day/acenocumarol	nsp	nsp	nsp	nsp
Pugnet et al. 2016 (68)	48.9±14.8	nsp	103	GC + statins (6 mo before index date)	n=606 sex- and age-matched controls with GC treatment (no PMR or vasculitis)	GC + statins	39.3±19 mo (statin exposure)	nsp	nsp	nsp
Pugnet et al. 2015 (69)	48.9±14.8	nsp	103 (29 included in fu analysis)	GC + statins (6 mo before index date)	n=606 sex- and age-matched controls with GC treatment (no PMR or vasculitis)	GC + statins	21.1±14.4 mo (statin exposure)	nsp	nsp	nsp
Narváez et al. 2007 (70)	3.6 years (range 1.1-15.1 years)	nsp	30	GC + statins	N=91 GC and not exposed to statins	GC (40-60 mg/day PRED equivalent or 1 g daily for 3 days in visual manifestation (n=5) + statins	nsp	Taper after resolution of symptoms and normalization of inflammatory markers	nsp	nsp
GarcÍa-martÍnez et al. 2004 (71)	2.8 years (range 9 mo-6.7 years)	nsp	17	GC + statins	N= 37 GC and not exposed to statins	GC 1 mg/kg/day (up to 60 mg/day) 1 mo + statins (for at least 12 mo	nsp	After 1 mo taper by 10 mg/week→ 20 mg/day→ taper slower and individualized→ 10	If ESR > 40 GC dose withold. If symptoms	nsp

						started before GCA diagnosis or in the first year of GC therapy)		mg/day over 2 mo→ 7.5 mg/day after 3 mo	(cranial manifestations or PMR), malaise or anemia GC increase by 10 mg/day above previous dose	
Alba et al. 2014 (72)	7.8±3.3 years	nsp	106 (n=36 ACEI, n=14 ARB)	GC + ACEI or ARB	N=79 GC and not exposed to ACEI or ARB (group 3)	GC 1 mg/kg/day (up to 60 mg/day) 1 mo or 1 g/day for 3 days in recent visual loss (< 48 h) + ACEI (group 1) or ARB (group 2): for at least 12 mo started before GCA diagnosis or in the first year of GC therapy	At least 12 mo (ACEI or ARB)	After 1 mo taper by 10 mg/week→ 20 mg/day for 1-2 weeks→ 15 mg/day for 1 mo→ 10 mg/day→ 7.5 mg/day after 3-6 mo→ slower reduction	↑ GC by 10-15 mg above previous effective dose +/- MTX 15 mg/week if ≥ 2 relapses or GC side effects	-ASA 20 (56%) group 1; 9 (64%) group 2; 24 (43%) group 3 -Statins 13 (56%) group 1; 4 (20%) group 2; 23 (41%) group 3

5.1.1.4 Supplementary Table 77. Adjunctive therapy/prophylaxis: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Disease duration at treatment start	Primary outcome	Results in active treatment group	Results in control group	p-value
Salvarani et al. 2009 (62)	74±7	138	GCA TAB+	nsp	-effect of anti-platelet/anticoagulant on cranial ischaemic events	10/37 (27%) treated with anti-platelet/anticoagulant had ischaemic events	16/140 (11.6%) did not have ischaemic events	nsp
Berger et al. 2009 (63)	73±8	60%	GCA newly diagnosed (TAB+ 78%)	nsp	-ASA as covariate of ischaemic events (68%)	-uOR 0.68 (95%CI 0.23-1.99) -aOR (for all other covariates) 0.87 (95%CI 0.25-3.08)	na	0.49 0.83
					-ASA as covariate of severe ischaemic events (32%)	-uOR 0.85 (95%CI 0.30-2.39) -aOR (for all other covariates) 0.86 (95%CI 0.25-2.96)	na	0.76 0.81
					-platelet count and volume	Detailed OR on paper (not relevant for treatment outcome)	na	0.52 0.91
Narváez et al. 2008 (64)	74±7	84	GCA newly diagnosed (TAB+ 73%)	3.2 mo	-ASA/anti-platelet on risk of severe ischemic events	9 (24.3%)	25 (29.8%)	0.54 Not significant for visual manifestations, cerebrovascular accidents ischaemic heart disease, limb claudication)
					-Relapse	48 (57.1%)	18 (48.6%)	0.40
					-recovered	25 (67.5%)	60 (71.4%)	0.66
Lee et al. 2006 (65)	71.8	109 (76%)	GCA (TAB+ 73%)	53.8 mo vs 46.7 mo	-Ischaemic events (31.5% vision loss, 4.2% strokes)	11 (16.2%)	36 (48%)	<0.0005

Nesher et al. 2004 (66)	76.1±7.5 vs 73.5±8.7	Ratio 1.4	Newly diagnosed GCA	nsp	-Ischaemic events at diagnosis	3 (8%)	40 (29%)	0.01 OR 0.22 (95%CI 0.06–0.80, *P* 0.02).
					-Ischaemic events during fu (3 mo)	3%	13%	0.02 OR 0.18 (95% CI 0.04–0.84, *P* 0.03).
Gonzalez-Gay et al. 2004 (67)	75	113	Newly diagnosed GCA	nsp	-Ischaemic events with or without anti-aggregants/anti-coagulant before diagnosis of GCA	nsp	nsp	nsp
Pugnet et al. 2016 (68)	74.8 vs 74.7	80 (77.7%) vs 469 (77.4%)	GCA newly diagnosed	nsp	-Statin effect on CVD hospitalization	HR 0.993 (95%CI 0.986-0.999)	na	0.0467
Pugnet et al. 2015 (69)	74.8 vs 74.7	80 (77.7%) vs 469 (77.4%)	GCA newly diagnosed	nsp	-Time to PRED maintenance dose	HR 1.6 (95%CI 0.97-2.72)	na	0.067
					-Frequency of PRED maintenance dose	HR 1.9 (95%CI 1.16-3.15)	na	0.011
Narváez et al. 2007 (70)	73.3±7.4 vs 74.8±7.6	23 vs 61	GCA (TAB+ 73%)	nsp	-Ischaemic events	Details on each event	Details on each event	ns
					-Aortitis	2 (7%)	7 (8%)	0.85
					-Relapses (statins vs not statins)	20 (67%	46 (50%)	0.24
					-Recovered from GCA	22 (73%)	63 (69%)	0.62
					-Duration of therapy	38.2±24.8 vs	33.5±33.1	0.64
GarcÍa-martÍnez et al. 2004 (71)	76 (range 57-91)	38	GCA (TAB+)	24 weeks vs 17 weeks	-Time to reach maintenance GC < 10 mg/day	Median 40 weeks (95%CI 21-59)	27 weeks (95%CI 22-32)	0.39
					-Dose GC before maintenance	5.81±2.1 g	5.7±2.3 g	0.87
					-Relapses	5 (29.4%)	19 (51.3%)	OR 2.4 (95%CI 0.71-8.15), P=0.24
					-ESR/CRP values	On figure	On figure	ns

Alba et al. 2014 (72)	75±7	37%	GCA (TAB+)	18±27 (group 1; ARB) vs 22±28 (group 2; ACEI) vs 15±19 (group 3; None)	-Relapses	adjHR 0.32 (95%CI 0.12-0.81)	na	0.017
					-N relapses ≥ 3 times	N=0 (ARB) vs 6% (ACEI)	21%	0.02
					-Time to GC < 10 mg/day with no relapse > 3 mo	On figure	On figure	0.0002
					-Time to GC < 5 mg/day with no relapse > 3 mo	Median 123 weeks (ACEI) vs 102 (ARB)	104	ns
					-Time to GC discontinuation	166 weeks (ACEI) vs 131 (ARB)	203	ns
					-Cumulative GC dose until < 10 mg/day	2.4±2.2 g (ACEI) vs 1±0.9 (ARB)	1.6±1.8	0.05
					-Cumulative GC dose first year	6.1±1.15 g (ACEI) vs 5.1±0.65 (ARB)	6±1.5 g	0.08
					ESR/CRP/haptoglobin	Not shown	Not shown	ns

5.1.1.5 **Supplementary Table 78. Adjunctive therapy/prophylaxis: safety/events**

Study ID	Type of AE/event	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for	Predictors/associated factors
Salvarani et al. 2009 (62)	Not applicable	na	na	na	na	na	na	na	na	na	na
Berger et al. 2009 (63)	Not assessed	na	na	na	na	na	na	na	na	na	na
Narváez et al. 2008 (64)	Related to ASA/anti-platelet	0	na	na	na	na	na	na	na	na	na
Lee et al. 2006 (65)	Bleeding	8	2	5	na	na	na	na	na	na	na

Nesher et al. 2004 (66)	Not assessed	na	na	na	na	na	na	na	na	na	na
Gonzalez-Gay et al. 2004 (67)	Not assessed	na	na	na	na	na	na	na	na	na	na
Pugnet et al. 2016 (68)	Not assessed	na	na	na	na	na	na	na	na	na	na
Pugnet et al. 2015 (69)	Not assessed	na	na	na	na	na	na	na	na	na	na
Narváez et al. 2007 (70)	Not assessed	na	na	na	na	na	na	na	na	na	na
García-martínez et al. 2004 (71)	Not assessed	na	na	na	na	na	na	na	na	na	na
Alba et al. 2014 (72)	Not assessed	na	na	na	na	na	na	na	na	na	na

5.1.1.6 **Supplementary Table 79. Adjunctive therapy/prophylaxis: risk of bias assessment (Newcastle-ottawa scale for cohort studies)**

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two *)
Salvarani et al. 2009 (62)	*	na	*	*	na	Self-report	nsp	*	4
Berger et al. 2009 (63)	*	*	nsp	*	**	Self-report	nsp	nsp	5
Narváez et al. 2008 (64)	*	*	no	*	*	Self-report	*	nsp	5

Lee et al. 2006 (65)	*	*	no	*	no	Self-report	*	nsp	4
Nesher et al. 2004 (66)	*	*	no	*	no	Self-report	*	*	5
Gonzalez-Gay et al. 2004 (67)	*	na	no	*	na	Self-report	nsp	nsp	2
Pugnet et al. 2016 (68)	*	*	*	*	*	*	*	*	8
Pugnet et al. 2015 (69)	*	*	*	*	*	*	*	*	8
Alba et al. 2014 (72)	*	*	no	*	*	Self-report	*	*	6

5.1.1.7 **Supplementary Table 80. Adjunctive therapy/prophylaxis: risk of bias assessment (Newcastle-ottawa scale for case-control studies)**

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Exposure** 1)Ascertainment of exposure	**Total n of stars** (only comparability can have two ∗)
Narváez et al. 2007 (70)	no	nsp	nsp	∗	no	∗	2
García-martínez et al. 2004 (71)	no	nsp	nsp	∗	no	∗	2

5.1.2 META-ANALYSIS (ASA)

5.1.2.1 Supplementary Table 81. Evidence retrieved for the use of antiaggregants in giant cell arteritis: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	End of follow-up for analysis	Included studies
ANTI-AGGREGANTS – META-ANALYSIS						
GCA						
Martínez-Taboada et al. 2014 (73)	Meta-analysis of observational studies	2a	To evaluate the effect of antiplatelet/anticoagulant therapy on the occurrence of severe ischemic complications in GCA at diagnosis and while on treatment with GC and the risk of bleeding.	Articles that included patients with GCA and data on the effect antiplatelet/anticoagulant therapy on the occurrence of severe ischemic complications	1992-December 2012	-Nesher et al. 2004 -Gonzalez-Gay et al 2004 -Lee et al 2006 -Narvaez et al 2008 -Salvarani et al. 2009 -Berger et al 2009

Mollan et al. 2014 (74)	Meta-analysis	NO RCTs FOUND, NO RESULTS	Assess the safety and effectiveness of low-dose ASA as an adjunctive in treatment of GCA	RCTs comparing outcomes of GCA with and without concurrent adjunctive low-dose ASA	Up to 24th January 2014	Very comprehensive SLR

5.1.2.2 Supplementary Table 82. Antiaggregants: outcome definition and statistical analysis

Study ID	Outcome/endpoint	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event
Martínez-Taboada et al. 2014 (73)	1)Effect of antiplatelet/anticoagulant on severe ischaemic complications in GCA at diagnosis and during GC therapy 2)Risk of bleeding	-Ischaemic events: as stated in single articles (all included visual loss and cerebrovascular events), variable on transient events, limb claudication or ischaemic heart disease	Single studies	GRADE quality	nsp

5.1.2.3 Supplementary Table 83. Antiaggregants: intervention

Study ID	Follow-up duration	Overall n. of patients	Active treatment group	n. of patients	Control group	n. of patients	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Martínez-Taboada et al. 2014 (73)	No pooled data	914	Antiplatelet/anticoagulants before diagnosis or after diagnosis + GC	204 (24.3%)	na	No pooled data	nsp	nsp	nsp	No pooled data

5.1.2.4 Supplementary Table 84. Antiaggregants: population characteristics and control and comparison

Study ID	Age	% females	GCA subtype	Primary outcome	Results in active treatment group	Results in control group	p-value
Martínez-Taboada et al. 2014 (73)	No pooled data	No pooled data	GCA newly diagnosed and fu	-Antiplatelet/anticoagulant before diagnosis of GCA	Funnel plot with single studies (ASA protects, ASA risk)	na	OR 0.661; 95%CI 0.287-1.520); p=0.33
				-Antiplatelet/anticoagulant after diagnosis of GCA	Funnel plot with single studies (ASA protects, ASA risk)	na	OR 0.318 (95%CI 0.101-0.996); p=0.049

5.1.2.5 Supplementary Table 85. Antiaggregants: safety/events

Study ID	Type of AE/event/outcome	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	p-value	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for
Martínez-Taboada et al. 2014 (73)	Bleeding events	nsp	Funnel plot with single studies (ASA protects, ASA risk)	na	0.089–4.856	OR	0.658	0.682	na	na	na

5.1.2.6 Supplementary Table 86. Antiaggregants: risk of bias assessment (AMSTAR tool)

Study ID	Was a priori design provided?	Duplicate study selection and data extraction?	Comprehensive literature search	Status of publication (grey literature) used as inclusion criteria?	List of studies provided?	Characteristics of the studies provided?	Scientific quality of the included studies assessed and	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies	Likelihood of publication bias assessed?	Conflict of interest included?

			perfor med?				documented ?		appropriate ?		
Martínez-Taboada et al. 2014 (73)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No

5.2 OBSERVATIONAL STUDIES (infections prophylaxis)

5.2.1 Pneumocystis jirovecii pneumonia

5.2.1.1 Supplementary Table 87. Evidence retrieved for infections prophylaxis in giant cell arteritis: overview of included studies

Study ID	Study design	Level of evidence	Overview	Inclusion criteria	Exclusion criteria	End of follow-up for analysis
GCA						
Infections/safety						
Pneumocystis jirovecii pneumonia						
Prospective						
Berger et al. 2015 (75)	Prospective cohort, single centre	4	Risk factors for pneumocystis jiroveci pneumonia (PCP) in newly diagnosed GCA	Consecutive newly diagnosed GCA (no details on diagnosis)	Fu < 2 mo	nsp
Retrospective						
Kermani et al. 2011 (76)	Retrospectiv e case series	4	Frequency, clinical presentation lab findings and outcome of PCP in GCA	TAB+ GCA who developed PCP	No clear identification of PCP	January 1976-December 2008

5.2.1.2 Supplementary Table 88. Infections prophylaxis: outcome definition and statistical analysis

Study ID	Outcome/endpo int	Definition of outcome	Validation of outcome	Notes on analysis	Censoring at event

Berger et al. 2015 (75)	nsp (Frequency and predictors of PCP infection)	-PCP infection: microbiological detection using immunofluorescence on BAL samples	Physician, microbiological analysis	Standard statistics (ANOVA, Spearman Rank)	nsp
Kermani et al. 2011 (76)	Clinical presentation, lab findings, outcome of PCP in TAB+GCA	-PCP: by smear or polymerase chain reaction (PCR) in sputum, BAL fluid, or lung biopsy specimens.	ICD-9 codes, microbiological identification	nsp	nsp

5.2.1.3 Supplementary Table 89. Infections prophylaxis: intervention

Study ID	Follow-up duration	Patient-years	Overall n. of patients	Intervention	Control	Treatment group	Duration of treatment	Treatment taper	Treatment of relapse	Adjunctive treatment
Berger et al. 2015 (75)	363 days (range 61-1429)	nsp	62 (4 PCP cases)	Standard care GC +/- MTX (relapse or GC resistant) +/- Trimethoprim/ sulphametoxazole	na	GC 20-50 mg/day + MTX 15-20 mg/week (at PCP infection)	nsp	nsp	Add MTX	Trimethoprim/sulphametoxazole in 30% of patients with GC+MTX vs 13% on GC alone
Kermani et al. 2011 (76)	nsp	nsp	7	Standard care	na	GC 30-80 mg (at PCP infection)	3 mo (1-18 mo)	nsp	nsp	nsp

5.2.1.4 Supplementary Table 90. Infections prophylaxis: population characteristics and control and comparison

Study ID	Age	% females	LVV subtype	Disease duration at treatment start	Primary outcome	Results in active treatment group	Results in control group	p-value
Berger et al. 2015 (75)	nsp	nsp	Newly diagnosed GCA	nsp	-PCP infections	4 (6%)	na	na
					-Associated factors	-lymphocytopenia		0.07 (PCP vs non-PCP)

						-GC cumulative dose (on figure)	na	0.75
Kermani et al. 2011 (76)	71.6±6	5	GCA (TAB+)	nsp	-PCP infections	7	na	na
					-Clinical presentation	Dyspnea (86%), pulmonary examination abnormal (57%), hypoxia (57%), lung infiltrates chest x-ray (71%)	na	na
					-outcome	ICU (57%), mechanical ventilation (43%)	na	na

5.2.1.5 Supplementary Table 91. Infections prophylaxis: safety/events

Study ID	Type of AE/event	N/% of events	N cases in treatment group	N cases in control group	Incidence rate (95% CI)	Type of ratio	uHR (I vs C)	Age/gender aHR (I vs C)	aHR (I vs C)	Adjusted for	Predictors/associated factors
Berger et al. 2015 (75)	Mortality	1	na	na	na	na	na	na	na	na	na
Kermani et al. 2011 (76)	Mortality	2 (29%)	na	na	na	na	na	na	na	na	na

5.2.1.6 Supplementary Table 92. Infections prophylaxis: risk of bias assessment (Newcastle-ottawa scale for cohort studies)

Study ID	**Selection** 1)Representativeness of exposed cohort	**Selection** 2)Selection of the non-exposed cohort	**Selection** 3)Ascertainment of exposure	**Selection** 4)Demonstration that outcome of interest was not present at start of study	**Comparability** 1)Comparability of cohorts on the basis of the design or analysis	**Outcome** 1)assessment of outcome	**Outcome** 2)Was follow-up long enough for outcomes to occur	**Outcome** 3)Adequacy of follow up of cohorts	**Total n of stars** (only comparability can have two *)
Berger et al. 2015 (75)	*	na	*	*	na	nsp	nsp	nsp	3
Kermani et al. 2011 (76)	*	na	*	*	na	*	nsp	*	5

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