Treatment and Management

7

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Abstract

Treatment and management guidelines for GCA slightly vary between international and national task forces. Therefore, this chapter provides an overview on currently available recommendations of the EULAR task force last updated in 2018, the BSR and BHPR guidelines from 2010, the recommendations of the French Study Group for Large Vessel Vasculitis from 2016 and the guidelines of the Swedish Society of Rheumatology from 2019, which were identified in the literature and reviewed for this book chapter. Besides, the relevant EULAR recommendations for the use of glucocorticoids in rheumatic diseases from 2013 and for imaging from 2018 together with the interdisciplinary recommendations for FDG-PET/CT(A) imaging of the Cardiovascular and Inflammation and Infection Committees of the European Association of Nuclear Medicine (EANM), the Cardiovascular Council of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the PET Interest Group (PIG), endorsed by the American Society of Nuclear Cardiology (ASNC) from 2018 were assessed to summarize current evidence necessary for monitoring of GCA and its comorbidities.

Keywords

Guidelines · Management · Recommendations · Review

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Treatment and management guidelines for GCA slightly vary between international and national task forces. Therefore, this chapter provides an overview on currently available recommendations of the EULAR task force last updated in 2018 [1], the BSR and BHPR guidelines from 2010 [2], the recommendations of the French Study Group for Large Vessel Vasculitis from 2016 [3] and the guidelines of the Swedish Society of Rheumatology from 2019 [4] were identified in the literature and reviewed for this book chapter. Besides, the relevant EULAR recommendations for the use of glucocorticoids in rheumatic diseases from 2013 [5] and for imaging from 2018 [6] together with the interdisciplinary recommendations for FDG-PET/CT(A) imaging of the Cardiovascular and Inflammation and Infection Committees of the European Association of Nuclear Medicine (EANM), the Cardiovascular Council of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the PET Interest Group (PIG), endorsed by the American Society of Nuclear Cardiology (ASNC) from 2018 [7] were assessed to summarize current evidence necessary for monitoring of GCA and its comorbidities.

7.1 General Aspects

General recommendations can be divided into those for time of diagnosis, for monitoring of GCA and those concerning adverse events and comorbidities. Details from the above-mentioned recommendations and guidelines for each of these situations are summarized in Table 7.1. Although not specified in these recommendations, the aim of treat-to-target is important for GCA as for other chronic rheumatic diseases, too, with remission being defined as lack of disease activity as the principal target of disease management. However, an aortic aneurysm may develop even without detectable clinical activity, and even years after disease outset [8]. Such caveats have to be kept in mind as peculiar issues in the management of GCA, arguing for prolonged monitoring even without detectable disease activity over years.

First, treatment is recommended to be initiated as soon as diagnosis is made to prevent further complications. Comorbidities predisposing to an increased risk for worse course of the disease or adverse events to medications have to be considered before start of treatment (see Chap. 6). Patients and their carers should be fully informed about management and risks of treatment.

For monitoring, the EULAR task force recommends assessment of symptoms, clinical findings, and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels for monitoring of disease activity ([1] recommendation 10). For clinical examination, monitoring is primarily based on symptoms (like jaw and tongue claudication, visual symptoms, vascular claudication of limbs), clinical findings

(like bruits and asymmetrical pulses, polymyalgic symptoms, osteoporotic risk factors and fractures). The UK guidelines add a specific recommendation to pay particular attention to the predictive features of ischemic neuro-ophthalmic complications [2]. Concerning laboratory biomarkers, also the French guidelines do explicitly not recommend measuring biomarkers other than C-reactive protein,

Table 7.1 Summary of general recommendations concerning situation at diagnosis, monitoring of GCA for the purpose to optimize treatment, adverse events, and comorbidities. *AE* adverse event, *CRP* C-reactive protein, *CV* cardiovascular, *ESR* erythrocyte sedimentation rate, *GC* glucocorticoid, *LoE* level of evidence, *LoA* (0–10), level of agreement

Year	Recommendation	LoE	LoA (0–10)	Ref.
	At time of diagnosis			
2019/R2	It is vital not to delay treatment, for example while waiting for a temporal artery biopsy			[4]
2019/R1	GCs remain first line for the treatment			[4]
2013/R6	Before starting medium-/high-dose GC treatment consider comorbidities predisposing to AEs. These include diabetes, glucose intolerance, CV disease, peptic ulcer disease, recurrent infections, immune-suppression, (risk factors of) glaucoma, and osteoporosis. Patients with these comorbidities require tight control to manage the risk/benefit ratio	IV		[5]
2013/R1	Explain to patients (and their family and/or carers, including healthcare professionals) the aim of medium-/high-dose GC treatment, and the potential risks associated with such therapy	III		[5]
2013/R2	Discuss measures to mitigate such risks, including diet, regular exercise, and appropriate wound care	III/IV		[5]
2013/R4	Patients and the patients' treatment teams should receive appropriate, practical advice on how to manage with GC-induced hypothalamic-pituitary-adrenal axis suppression	IV		[5]
2016/9b	The systematic initiation of treatment with intravenous methylprednisolone pulse(s) is not recommended		100	[3]
	Monitoring during follow-up			
2018/R10	Regular follow-up and monitoring of disease activity is recommended, primarily based on symptoms, clinical findings and ESR/CRP levels	3b	9.6 ± 0.6	[1]
2013/R5	Provide an accessible resource to promote best practice in the management of patients using medium-/high-dose GCs to general practitioners	IV		[5]

(continued)

Table 7.1 (continued)

Year	Recommendation	LoE	LoA (0–10)	Ref.
UK2010/R7a	Monitoring of therapy should be clinical and supported by the measurement of inflammatory markers. Patients should be monitored for evidence of relapse, disease-related complications, and GC-related complications. In particular, the following features should be sought: Jaw and tongue claudication, visual symptoms, vascular claudication of limbs, bruits and asymmetrical pulses, polymyalgic symptoms, osteoporotic risk factors and fractures, other GC-related complications, other symptoms that may suggest an alternative diagnosis The following investigations should be performed: At each visit: full blood count, ESR/CRP, urea and electrolytes, glucose. Every 2 years: chest radiograph to monitor for aortic aneurysm (echocardiography, PET and MRI may also be appropriate). Bone mineral density may be required Routine follow-up should be planned at: Weeks 0, 1, 3, 6, then Months 3, 6, 9, 12 in the first year. Later (Month 3 onwards) follow-up can be undertaken under shared care *Relapse:* Disease relapse should be suspected in patients with return of symptoms of GCA, ischemic complications, unexplained fever, or polymyalgic symptoms. All patients in whom relapse is suspected should be treated as below, and discussed or referred for specialist assessment. Return of headache should be treated with the previous higher dose of GC. Symptoms of large-vessel disease should prompt further investigation with MRI or PET and use of systemic vasculitis treatment protocols	C		[2]
2016/8a	CT or MRI screening for complications of aortitis is recommended at GCA diagnosis, then every 2–5 years, provided the patient has no contraindications to a potential aorta repair		93.8	[3]
2013/R8	Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of undertreatment, and development of AEs	IV		[5]
2016/15c	A purely biological "relapse" or "recurrence" does not necessarily require GC dose intensification or the initiation of adjunctive therapy but should prompt closer monitoring		96.8	[3]
2018/R10	In patients in whom a flare is suspected, imaging might be helpful to confirm or exclude it. Imaging is not routinely recommended for patients in clinical and biochemical remission	5	9.4 ± 0.8	[6]
2016/15a	For a first relapse or recurrence, treatment with GCs is recommended at a dose that depends on symptom severity and by at least returning to the previously effective dose		100	[3]

Table 7.1 (continued)

Year	Recommendation	LoE	LoA (0–10)	Ref.
2018/ R7a	In case of major relapse (either with signs or symptoms of ischemia or progressive vascular inflammation), we recommend reinstitution or dose escalation of GC therapy as recommended for new onset disease For minor relapses, we recommend an increase in GC dose at least to the last effective dose	2b	9.5 ± 1.0	[1]
	Adverse events and comorbidities			
2013/R3	Patients with, or at risk of, GC-induced osteoporosis should receive appropriate preventive/therapeutic interventions	IA		[5]
2013/ R10	All patients should have appropriate monitoring for clinically significant AEs. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems, and neuropsychological AEs	IV		[5]
2016/11a	GCA with uncomplicated and asymptomatic involvement of the aorta or its branches can be treated with the GC regimen recommended for uncomplicated GCA		90.3	[3]
2016/10b	The tapering schedule and duration of glucocorticoid treatment for GCA with ophthalmic involvement should follow the same regimen as that recommended for uncomplicated GCA		96.8	[3]

erythrocyte sedimentation rate, and fibrinogen for monitoring disease activity [3]. Additional laboratory biomarkers maybe necessary for monitoring of GCA complications, comorbidities, and adverse events of GCA-related treatment.

Concerning the imaging biomarkers, the EULAR recommendation for imaging states that imaging "might be helpful in patients with suspected flare, especially when clinical and laboratory parameters are inconclusive" and that "MRA, CTA and/or US may be used for long-term monitoring of structural damage, particularly to detect stenosis, occlusion, dilatation and/or aneurysms, on an individual basis" ([6] recommendation 10 and 11), while the other international consensus on imaging does definitely not support a value of FDG-PET/CT(A) for evaluating response to treatment [7]. It is argued that a positive ^{18}F-FDG-PET persists in up to 60% of patients in full clinical remission, and using sonography, residual changes often remain visible for several months in extracranial arteries.

Important to note, that—if necessary—times of stable remission should be selected for elective surgical interventions or reconstructive surgery (recommendation 9, [1]), while for emergency situations repair of an aortic lesion should be scheduled once the systemic inflammatory response has subsided [3].

7.2 Glucocorticoids as First-Line Treatment

Glucocorticoid (GC) therapy is still considered as first-line therapy in GCA, despite their multiple adverse events. GCs should be started immediately after diagnosis and information of the patient. If the symptoms of GCA do not respond rapidly to high-dose GC treatment, followed by resolution of the inflammatory response, the question of an alternative diagnosis should be raised.

Recommendations for optimal dosage and dose reduction of GCs differ between EULAR and national guidelines (Tables 7.2 and 7.3). EULAR experts start with 40–60 mg/day prednisone-equivalent for induction of remission in active GCA and recommend tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months and after 1 year to ≤5 mg/day. In case of signs and symptoms of reactivated disease, the dosage of GCs should be increased to the latest effective dose and GC-sparing agents be considered (see Sect. 7.3). Specific recommendations with higher dosage regimens apply to ocular and aortic aneurysmatic involvement (Table 7.3).

Monitoring is considered essential for treatment adaptions in GCA and includes: clinical signs and symptoms of GCA-activity and GCA complications,

Table 7.2 Recommendations concerning dosage of GCs, with specific recommendation for eye involvement. Important aspects are marked in bold letters. *GC* glucocorticoids

Year	Recommendation	LoE	LoA (0–10)	Ref.
EULAR 2018/R4	High-dose GC therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active GCA. Once disease is controlled, we recommend tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months and after 1 year to ≤5 mg/day	4 5	9.8 ± 0.6 9.5 ± 0.9	[1]
2019/R3	The recommended initial dose of prednisolone is 40–60 mg for 4 weeks, thereafter gradually tapered (until ESR and CRP have been normalized, and signs and symptoms have improved). Thereafter, reduction of the dose by 10 mg every other week to 20 mg daily. Thereafter, reductions of 2.5 mg with 2–4 week intervals to 10 mg daily. If there are no signs of relapse, the dose may be reduced by 1 mg every 1–2 months. After every dose reduction, the patient's ESR and CRP are checked and the return of signs and symptoms is also checked. If signs and symptoms of active disease return, the dose of prednisolone should be increased to the latest effective dose			[4]

Table 7.2 (continued)

Year	Recommendation	LoE	LoA (0–10)	Ref.
UK 2010/R4a	High-dose GC therapy should be initiated immediately when clinical suspicion of GCA is raised. Recommended starting dosages of GC are for uncomplicated GCA (no jaw claudication or visual disturbance): 40–60 mg prednisolone daily. The symptoms of GCA should respond rapidly to high-dose GC treatment, followed by resolution of the inflammatory response. Failure to do so should raise the question of an alternative diagnosis	C		[2]
2016/9a	We recommend treating uncomplicated GCA with oral prednisone at a starting dose of 0.7 mg/kg/day, then gradually tapering to reach 15–20 mg/day at 3 months, 7.5–10 mg/day at 6 months, 5 mg/day at 12 months and weaning off GCs within 18–24 months		100	[3]
UK 2010/R4b	GC reduction should be considered only in the absence of clinical symptoms, signs, and laboratory abnormalities suggestive of active disease. This should be balanced against the need to use the lowest effective dose, patient wishes, and GC side effects. Steroid reduction may also be appropriate if the acute-phase response is deemed to be due to another cause. Suggested tapering regimen: • 40–60 mg prednisolone continued until symptoms and laboratory abnormalities resolve (at least 3–4 weeks) • then dose is reduced by 10 mg every 2 weeks to 20 mg • then by 2.5 mg every 2–4 weeks to 10 mg • then by 1 mg every 1–2 months provided there is no relapse The dose may need adjustment for disease severity, comorbid factors, fracture risk, patient wishes, and adverse events. There are also some patients who will require long-term low-dose GC therapy	C		[2]
2016/11b	For complicated (dilatation, aortic aneurysm, or dissection) or symptomatic (limb claudication or ischemia) aortoarteritis at GCA onset, oral prednisone at 1 mg/kg/day can be prescribed as a starting dose		87.1	[3]
UK 2010/R7b	Relapse: • Jaw claudication requires 60 mg prednisolone	C		[2]
2018/3	Withdraw or delay GC therapy until after PET, unless there is risk of ischemic complications, as in the case of GCA with temporal artery involvement. FDG-PET within 3 days after start of GC is optional as a possible alternative	III	B	[7]

Table 7.3 Recommendations concerning dosage of GCs, with specific recommendation for eye involvement. Important aspects are marked in bold letters. *GC* glucocorticoids

Year	Recommendation	LoE	LoA (0–10)	Ref.
	Eye involvement			
Sweden 2019/R4	If vision is impaired or there are other signs of serious vascular involvement, intravenous methylprednisolone 1000 mg once daily for 3 days may be considered, followed by oral treatment as above			[4]
UK 2010/R4a	Recommended starting dosages of GC are: • Evolving visual loss or amaurosis fugax (complicated GCA): 500 mg to 1 g of i.v. methylprednisolone for 3 days before oral GCs • Established visual loss: 60 mg prednisolone daily to protect the contralateral eye	C		[2]
2016/10a	Suspected GCA with transient or permanent ophthalmic involvement should be treated immediately with 1 mg/kg/day of oral prednisone or 500–1000 mg/day of intravenous methylprednisolone for 1–3 days (followed by oral prednisone at 1 mg/kg/day), according to regimen that can be most rapidly initiated		100	[3]
UK 2010/R7b	Relapse: • Eye symptoms need the use of either 60 mg prednisolone or i.v. methylprednisolone	C		[2]

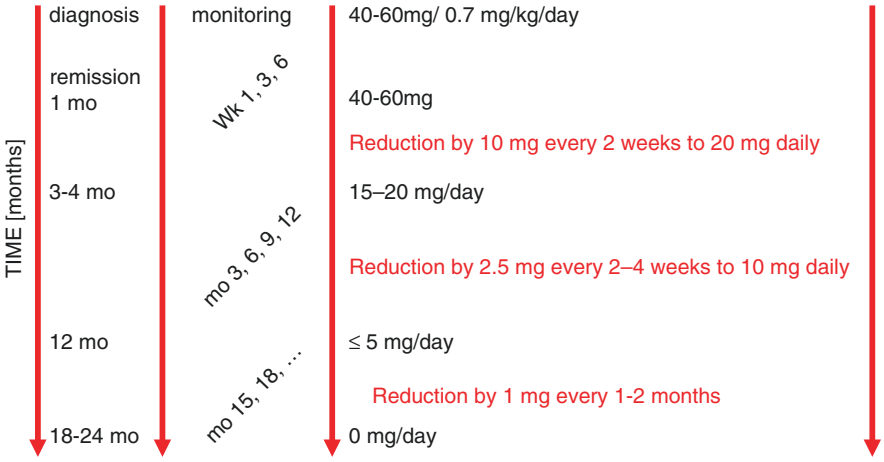

Fig. 7.1 Summary of GC schemes in recommendations and guidelines together with UK proposal for monitoring from 2010 (from Table 7.1). Dosages are given for prednisolone equivalents. Reductions of GCs (marked in red) should be recommended only in the absence of any signs and symptoms of GCA (recommendation summarized from Table 7.4). *Mo* months, *wk* week

treatment-related adverse events, and comorbidities. The schedule for monitoring in relation to recommended dosages of GCs is depicted in Fig. 7.1. For monitoring after 18 months of disease duration, further clinical schedules depend on residual disease activity. Chest radiographs, echocardiography, PET, or MRI are

recommended for early detection of an aortic aneurysm every 2–5 years, and additional bone mineral density may be needed.

Unfortunately, literature lays out that relapses of GCA under treatment with GCs occur in as many as 47.2% (95% confidence interval 40.0–54.3%) of patients, with more relapses reported in randomized-controlled trials (RCTs) than in observational studies and under shorter GC regimens (rate decrease of 1.7% for one additional month), but independent from initial GC doses (3). As a consequence, GCs alone appear to be insufficient for treatment of GCA in many patients, and GC-sparing agents may become necessary.

7.3 Glucocorticoid(GC)-Sparing Agents

Because of the wide spectrum of possible GC-related side effects, GC-sparing agents have always been considered as an important issue for treatment of GCA. Therefore, several synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs) have been studied for the GC-sparing effects (Table 7.4). Overall, use of a GC-sparing agent beside GCs has been shown to be a protective factor both against new CV events (HR 0.44 (95% confidence interval (CI) 0.29–0.66)) as well as the development of aortic dilatation (HR 0.43 (CI 0.23–0.77)) [9]. Thus, GC-sparing agents should be considered especially for patients with insufficient response to GCs alone and patients with pre-existing comorbidities or high risk of GC-related side effects.

Recently, a meta-analysis comparing different GC-sparing agents showed that the two drugs tocilizumab (TCZ), a biological (b)DMARD, and methotrexate (MTX), a conventional (c)DMARD can be considered as GC-sparing agents. Both GC-sparing agents resulted in improved likelihoods of being relapse free with relative risks of 3.54 for TCZ and 1.54 for MTX [10]. At present, the bDMARD TCZ is the only FDA- and EMA-approved GC-sparing agent for the treatment of GCA—as an IL 6 R antagonist it showed efficacy in induction of sustained remission in both a phase II [11] and a phase III study (the GIACTA trial, [12]). The GIACTA trial showed that the risk of flares during TCZ treatment weekly and every other week decreases compared to the placebo group (HR 0.23 (CI 0.11–0.46) and 0.28 (CI, 0.12–0.66), respectively). TCZ co-treatment also resulted in lower cumulative prednisolone doses during trial duration ($p < 0.001$). To be remembered as a challenge of monitoring, is the suppressive effect of TCZ especially on the CRP biomarker. For monitoring of TCZ, it is important to early detect increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5-fold upper limit of normal, absolute neutrophil counts lower than 0.5–1.0 × 10^9/L, and platelet counts lower than 50–100 × 10^3/μL [13–16]. Blood count, liver function test, and lipid parameters should be evaluated 4–8 weeks after initiation and at 6-month interval thereafter. Live and live-attenuated vaccines should not be given concurrently with TCZ. Although the safety profile of TCZ in GCA appears similar to placebo with comparable numbers of adverse events per 100 patient years, longer follow-up periods in RCT trial are needed to underline its benefit-to-harm ratio [17].

Table 7.4 Summary of a meta-analysis (MA), a comparative MA (CMA), and additional randomized-controlled trials (RCTs, patient number >25) on treatment options for GCA, including conventional as well as biological disease-modifying anti-rheumatic drugs (cDMARDs and bDMARDs, respectively). *ABA* Abatacept, *ADA* Adalimumab, *CI* 95% confidence interval, *cDMARD* conventional DMARD, *bDMARD* biological DMARD, *ETA* etanercept, *GC* glucocorticoid, *HR* hazard ratio favoring MTX, *IFX* infliximab, *MTX* methotrexate, *mo* months, *n.s.* not significant, *Pl* placebo, *RR* relative risk to improve likelihood of being relapse free, *TCZ* tocilizumab, *vs* versus, *wks* weeks

Drug	MA/ RCT	Patients total [*n*]	Duration [months]	Results	Ref.
cDMARDs					
• MTX	MA	161	55 ± 39 wks	HR 1st relapse 0.65 (CI 0.44–0.98) HR 2nd relapse 0.49 (CI 0.27–0.89)	[18]
• MTX	CMA	161	55 ± 39 wks	RR 1.54 (CI 1.02–2.30)	[10]
bDMARDs					
IL6R blockade	CMA	281	52 wks	RR 3.54 (CI 2.25–5.51)	[10]
• TCZ	RCT	251	12 mo	*Sustained remission* $p \leq 0.001$: 56% (56/100) TCZ weekly 53% (26/49) TCZ every other week 14% (7/50) Pl; 26-week GC taper 18% (9/51) Pl; 52-week GC taper	[12]
• TCZ	RCT	30	12 mo	*Sustained remission* $p = 0.001$: 85% with TCZ ($n = 17/20$) 20% with GC ($n = 2/10$)	[11]
CTLA4-blockade	CMA	41	12 mo	RR 1.50 (CI 0.71–3.17)	[10]
• ABA	RCT	41	12 mo	*Sustained remission* $p = 0.049$: 48% with ABA vs. 31% with Pl	[20]
TNF-blockade	CMA	131	22–52 wks	RR 1.12 (0.79–1.58)	[10]
• IFX	RCT	44	22 wks.	*Relapse free* $p = 0.65$: 43% with IFX vs. 50% with Pl	[23]
• ADA	RCT	70	6 mo	*Sustained remission* $p = 0.46$: 20 (59%) with ADA vs. 18 (50%) with Pl	[24]
• ETA	RCT	17	1 year	*Controlled disease* p = n.s.: 50% ETA and 22.2% placebo (n.s.)	[25]

As a consequence of this high level of evidence, the updated EULAR guidelines recommend that "adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC-related adverse events or complications) using TCZ." MTX is only considered as an alternative (Table 7.5). MTX is not approved for the treatment of GCA and although lower dosages have not been shown to be effective, two independent meta-analyses of current literature revealed a beneficial effect of MTX in GCA [10, 18].

Only a few other agents have been tested as possible GC-sparing agents so far [19]. Although a randomized-controlled trial showed that the bDMARD abatacept

Table 7.5 Recommendations concerning GC-sparing agents (from EULAR and other national taskforces as indicated). Recommendations published before approval of TCZ for the indication of GCA are not included into this table. *TCZ* tocilizumab

Year	Recommendation	LoE	LoA (0–10)	Ref.
EULAR 2018/R5	Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC-related adverse effects or complications) using TCZ MTX may be used as an alternative	1b 1a	9.4 ± 0.8 9.4 ± 0.8	[1]
EULAR 2018/R7b	Initiation or modification of adjunctive therapy should be considered particularly after recurrent disease relapses	1b	9.6 ± 1.0	[1]
Sweden 2019/R6	In cases of newly diagnosed GCA, TCZ may be considered when there is a great risk of future side effects of GCs and pronounced clinical and laboratory signs of vascular inflammation			[4]
Sweden 2019/R5	The rationale for treating GCA with TCZ is primarily its GC-sparing effect over time. TCZ is recommended as supplement to prednisolone treatment in patients with recurrent or active illness during GC treatment, providing the criteria of relapse during GC treatment or relapse after completion of treatment with GC, large-vessel arteritis verified at some point with biopsy or with imaging of large vessels (MRI, PET-CT, or CTA), clinically active GCA, elevated CRP and ESR or obvious side effects of GC treatment or great risk of such side effects from future treatment with GCs are met			[4]
Sweden 2019/R7	Treatment with TCZ should be discontinued after 1 year. Longer periods of treatment cannot be recommended with our present state of knowledge. If inflammation persists after 1 year of treatment with TCZ, an individual assessment must be made by the treating physician			[4]

(ABA), an inhibitor of the T-cell receptor CTLA4, may be useful to maintain remission in GCA-patients [20], ABA was not so effective in this trial. Another open-label study suggested that the bDMARD ustekinumab, which targets the interleukins IL12 and IL23, could be useful for the treatment of patients with refractory GCA [21]. In cultured GCA arteries, inhibition of IL-12/IL-23p40 tended to reduce IFNγ and IL-17 mRNA production and to increase the Th17 inducers IL-1β and IL-6 [22]. Now, further studies are required to assess whether ABA and ustekinumab extend our repertoire of adjunctive therapies to reduce relapses or as a GC-sparing agents in GCA. The interleukin-1 binding bDMARD, anakinra has been successfully used only in a few patients with refractory GCA. Blockade of TNF-alpha turned out already earlier to be ineffective as a GC-sparing approach [23, 24].

7.4 Treatment of Comorbidities/Adjuvant Therapies

Comorbidities may occur as a consequence of higher age, as complications of GCA itself and GCA-treatment. For optimal treatment of GCA-patients, all of these issues have to be considered, and deterioration of only one of the comorbidities may result in severe complications with increased morbidity or even mortality.

Although treatment of comorbidities is essential for the optimal outcome of GCA, only a few recommendations refer to comorbidities (Tables 7.6):

1. Concerning the recommendations on antiplatelet and anticoagulant therapy, low-dose aspirin is advised or at least should be considered for GCA-patients without contraindication according to national guidelines, but the EULAR task force recommends low-dose aspirin or at least to consider it only for patients with other indications or in special situations (Table 7.6).
2. Bone protection is recommended by the UK guidelines for GCA.
3. Proton pump inhibitors for gastrointestinal protection should be considered according to the UK guidelines for GCA.
4. The systematic prescription of statins is not recommended by the French guidelines for GCA.
5. Recent evidence confirms the use of GC-sparing agents to reduce GCA-related comorbidities (see Sect. 7.3). Besides, monitoring is recommended especially for osteoporosis, CV-risk factors (including arterial hypertension and diabetes mellitus), and CV disease.

Further recommendations for other comorbidities are not included in the available EULAR and national GCA-specific recommendations, so that risk and comorbidity-specific recommendations have to be adapted for GCA-patients. For example, the risk of infections is estimated to be twofold increased in GCA-disease [26, 27], with the need of appropriate patients' information, monitoring and treatment, independent from the GCA-specific recommendations.

Table 7.6 Recommendations for additional treatments in GCA. *LoE* level of evidence, *LoA* level of agreement

Year	Recommendation	LoE	LoA (0–10)	Ref.
EULAR 2018/R8	Antiplatelet or anticoagulant therapy should not be routinely used unless it is indicated for other reasons (e.g., coronary heart disease or cerebrovascular disease). In special situations, such as vascular ischemic complications or high risk of cardiovascular disease, these might be considered on an individual basis	4	9.4 ± 0.8	[1]
France 2016/14a	Low-dose aspirin (75–300 mg/day) should be considered for every patient with newly diagnosed GCA upon benefit–risk assessment; for GCA with ophthalmic involvement, prescribing low-dose aspirin should be advised		100	[3]
UK 2010/R5	Low-dose aspirin should be considered in patients with GCA if no contraindications exist	C		[2]
France 2016/10c	Aspirin (75–300 mg/day) should be advised for GCA with ophthalmic involvement		96.8	[3]
France 2016/14b	The systematic prescription of an anticoagulant or a statin is not recommended		93.5	[3]
UK 2010/R4a	Patients should also receive bone protection. Proton pump inhibitors for gastrointestinal protection should be considered	C		[2]

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