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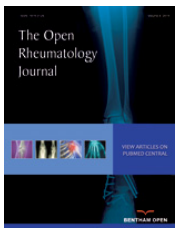

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RESEARCH ARTICLE

Steroid-Sparing Agents in Giant Cell Arteritis

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Abstract:

Background:

Giant cell arteritis is the commonest form of medium-to-large vessel vasculitis, requiring long-term corticosteroid therapy. The short- and long-term side effects of corticosteroids are many, including weight gain, psychological effects, osteoporosis, cardiometabolic complications, and infections.

Materials and Methods:

Various agents used in place of or in combination with corticosteroids to reduce corticosteroid-related side effects were reviewed. However, considerable variation in practice was identified giving unclear guidance. This review included the most recent evidence on methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, abatacept, and tocilizumab

Results and Discussion:

Also discussed are encouraging results with tocilizumab in GCA patients. Amongst the agents available for steroid-sparing effects, tocilizumab demonstrated the most robust data and is consequently recommended as the agent of choice for steroid-sparing, for remission induction, remission maintenance, and treating relapsing and refractory cases of GCA.

Keyword: Corticosteroids, Tocilizumab, Giant cell arteritis, Vasculitis, Steroid-sparing, EULAR, Epidemiology.

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1. INTRODUCTION

Giant Cell (temporal) Arteritis (GCA) is a chronic, systemic vasculitis, with a distinct tropism for large and medium-sized arteries with well-developed elastic membranes. The epidemiology of GCA suggests striking differences in disease risk among ethnic groups, with the highest incidence rates found in Scandinavian and other people of Northern European descent, irrespective of their place of residence [1 - 5]. Globally, the incidence of GCA is around 27 per 100,000 in persons over 50 years of age [6]. Corticosteroids are the mainstay of therapy. Prompt diagnosis and initiation of therapy is critical to prevent complications such as partial visual loss or blindness and other vascular complications [7 - 11]. The average duration of corticosteroid therapy in GCA is 2-3 years, although lifelong treatment may be required in some patients [8, 12 - 15].

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Long-term corticosteroid use (3-6 months or more) is potentially associated with treatment-related Adverse Events (AEs), however, the incidence and severity are commonly dependent on a combination of the daily dose and regimen cumulative dose [15 - 18]. These AEs include skin, gastrointestinal, ophthalmological, skeletal, adrenal, cardio-metabolic, and neuropsychiatric complications [13, 17, 19]. The corticosteroid-related AEs patients and rheumatologists consider the most worrisome include weight gain, psycho-logical effects, osteoporosis, and infections [20].

Given the substantial morbidity associated with long-term corticosteroid therapy, guidelines (*e.g.*, from the European league against rheumatism [EULAR] and British Society for Rheumatology) recommend that steroid-sparing agents should be used [21], but as evidence is limited, there are variations in the treatment strategy and no specific guidance available about the agent choice for this diverse group of patients.

This critical review of the literature examines evidence on agents that, if used may reduce the required steroid dose or the

duration of steroids treatment and decrease the frequency and/or intensity of patient experienced side effects.

2. MATERIALS AND METHODS

The databases searched were; Medline®, Cochrane library and EMBASE® using the keywords <steroid sparing effects>, <methotrexate>, <mycophenolate mofetil>, <cyclophosphamide>, <azathioprine>, <anti-TNF agents>, <abatacept>, <selective T cell co-stimulation modulator> and <tocilizumab> and <Giant Cell Arteritis>. The limits applied were from 2000 onwards and articles in the English language, and adult population. Relevant natural language and controlled vocabulary terms were selected and combined. Where possible, articles were restricted to systematic reviews, RCTs or case series.

3. RESULTS AND DISCUSSION

3.1. Variations in the Optimal Treatment Strategies for GCA

In a large, representative cohort of real-world patients seen in routine clinical practice of rheumatologists across the United States of America, treatment patterns were reviewed using data from electronic medical records and other sources in an ongoing and continuous updating manner. These patients met the definition of at least two GCA-related diagnosis codes within a 1-year period, between 2013 and 2016. Amongst 1567 patients with a mean age of 72+10 years, 78% were Caucasian and 78% were females. The mean follow-up period was 24 months with an average of 12 Rheumatology clinic visits. There were 14% of all patients treated with more than one agent concurrently, and 85% received corticosteroids. This study demonstrated that there was wide variation in treatment practices where 22% of patients treated with methotrexate, 8% with hydroxychloroquine, 5% with aspirin, 5% with tocilizumab, and 3.5% with azathioprine [6]. This also reflects the lack of clarity around the value of additional steroid-sparing agents to avoid [6] corticosteroids.

3.2. Relapsing and Refractory GCA

The traditional view of GCA as a corticosteroid-responsive disease is not always accurate or predictable; a spectrum of severity and extent exists. In observational cohort studies, relapses were reported in 34-62% of patients, with 15-20% achieving long-term sustained remission with corticosteroids alone [22]. Based on treatment response, GCA patients can be divided into four subgroups; in-remission, relapsed, refractory, and corticosteroid intolerant [3]. The last three groups exhibit the greatest unmet need for adjunctive therapy [22]. A critical review of the literature published in Clinical and Experimental Rheumatology [23] revealed five case series with large cohorts. These suggested that 40-48% of GCA patients require additional immunosuppressive agents to achieve remission and to taper their corticosteroid intake.

3.3. Methotrexate and Steroid-Sparing Effect

Methotrexate (MTX) efficacy and safety was evaluated in patients with GCA enrolled in three randomized clinical trials. These reported inconsistent efficacy, but reductions in relapse rate and in overall corticosteroids exposure [24 - 26]. In a meta-analysis of individual patient data from these trials, it was found that adjunctive low-dose MTX reduced both relapse risk and corticosteroids exposure, though the frequency and severity of AEs were not reduced [27, 28]. Adjunctive MTX may reduce cumulative corticosteroids doses by 20% [25] and relapses by 35% (28) in GCA. Similar beneficial effects were observed to reduce corticosteroids dose and a reduction in relapses [23]. Based on a systematic analysis of clinical trial data, the use of MTX as a steroid-sparing strategy may be considered for patients at high risk for corticosteroid-induced AEs at disease outset. It may also be useful for patients whose disease course is protracted and who are at risk for recurrent relapses and corticosteroid-induced AEs [29, 30].

3.4. Mycophenolate Mofetil

In a retrospective study (n=65 GCA patients), patients were divided into 3 treatment groups; prednisolone alone, prednisolone with methotrexate, and prednisolone with mycophenolate (MMF). No significant difference was shown between the groups. The study concluded that MMF is as effective as MTX and prednisolone alone in the treatment of Large Vessel Vasculitis (LVV). However, the patient group was small which limits the generalisation of this finding. Additionally, there was no randomisation to the treatment group; treatment choice was based on clinician preference. There was potential bias in that patients perceived to be more difficult to treat may have been given MMF or MTX in addition to prednisolone, and there were a higher proportion of patients with LVV compared to GCA in the MMF and MTX treated groups [31 - 34].

3.5. Azathioprine

A two-centre retrospective study was designed to describe the use of azathioprine in GCA and to evaluate its steroid-sparing effect. Of the 28 patients included, 21 responded to the combination of azathioprine and prednisolone [35]. At 1 year of follow-up from the initiation of azathioprine and a daily dose of prednisone, 18 patients (64%) were still in sustained response, asymptomatic, and showed no increase in acute phase response laboratory markers. Three patients (11%) experienced a relapse during azathioprine treatment. The mean daily dose of prednisone was 25.4 mg at the time of initiation of azathioprine, and 4.7 mg at 1 year of treatment, suggesting a good steroid-sparing effect [35]. Treatment cessation was required in 7 out of 10 patients who experienced azathioprine-related serious side effects. It was concluded that azathioprine may be an alternative treatment for patients with GCA requiring prolonged high dose corticosteroids therapy or developing severe corticosteroid related side effects [35].

3.6. Cyclophosphamide

Data from 19 patients treated with cyclophosphamide (CYC) were retrospectively analysed. In 15 of the 19 patients, CYC had been administered after the failure of high doses of corticosteroids, or experiencing a relapse during medium to high dose corticosteroids therapy, with or without MTX [36]. CYC was used as the initial treatment in corticosteroid naive patients (4 of the 19 patients). All of the participants were also

diagnosed with type 2 diabetes. During the 6-12 months follow-up, 15 of the 19 patients remained in remission. Corticosteroids were suspended in 6 of the 15 patients, and a dose of 5 mg/day of prednisone was continued in 9 patients. Relapse occurred in 4 of the 15 patients who sustained remission, usually 12 months after CYC was ceased. The cessation or reduction of their corticosteroid daily dose or reduction to 5 mg/day of prednisone took place within the first 6 months of follow-up after the initiation of CYC in 10 of the 15 patients. Ten adverse events were registered in nine patients, with recovery soon after the suspension of CYC or dose reduction [36]. However, one death occurred due to acute hepatitis. The disappearance of inflammatory infiltrate was demonstrated in one patient when temporal artery biopsy was repeated 3 months after CYC therapy. This study concluded that CYC could represent a useful option for patients requiring prolonged medium- to high-dose of corticosteroid therapy and at high risk of corticosteroids-related side effects (36).

3.7. Anti-TNF Agents and their Steroid-Sparing Effect in GCA

A systematic review [37] was conducted to evaluate the efficacy and safety of infliximab and etanercept in LVV. This review concluded that infliximab was not more effective than corticosteroids in inducing remission in GCA patients, but it was effective in inducing remission and in steroid-sparing in corticosteroid refractory Takayasu's arteritis. The review concluded that etanercept has a role as a steroid-sparing agent in GCA with corticosteroid related sever`l`e adverse effects and is effective in inducing remission in corticosteroid refractory GCA [37].

3.8. Abatacept (Selective T cell Co-Stimulation Modulator) and Steroid-Sparing in GCA

Abatacept, a selective T cell co-stimulation modulator [38], was recently evaluated in a multicentre, randomized, double-blind (phase 2) trial of 49 patients with GCA who received a standardized prednisone tapering regimen [20]. Patients' selection criteria were temporal artery abnormality, a biopsy demonstrating vasculitis, and characteristic changes of large-vessel stenosis or aneurysm on arteriography. Additionally, those with large-vessel involvement underwent MRI of the aorta and branches initially and at 6-month intervals. At 12 months, the relapse-free rate was significantly higher in the abatacept group than in the placebo group (48 *vs* 31%; $P = 0.049$), and a longer median duration of remission was achieved with abatacept (9.9 *vs* 3.9 months; $P = 0.023$). Despite the small number of patients with large-vessel involvement in this study population, the findings suggest that abatacept may be an efficacious treatment option for reducing relapse in patients with GCA, but comparative studies will be required to determine its place in therapy.

3.9. IL-6R Antagonist (Tocilizumab) and Steroid-Sparing Effect in GCA

Interleukin (IL)-6 contributes to the pathogenesis of GCA and represents a possible target for therapy. A retrospective study of 12 patients, with relapsing GCA history, were treated with monthly infusions of the IL-6 receptor (IL-6R) antagonist tocilizumab (TCZ). The average daily prednisone dose decreased from 24 mg (95% CI 15-33.5) at the time of TCZ initiation to 7.3 mg (95% CI 0.7-14) by the time of last evaluation ($P = 0.01$) [39]. The mean follow-up of this cohort since diagnosis was 37 months. Out of all the patients who received TCZ, 7 patients were in disease remission until the end of follow-up for a mean time of 17.5 months (range 8-26), and 5 patients experienced a flared after an average of 11 months of therapy (range 2-25). It was concluded that TCZ led to a significant decrease in the flare rate and requirement for corticosteroid use in the study sample. These findings supported that TCZ is a steroid-sparing agent during treatment and in GCA remission [39, 40]. GiACTA, a randomized, double-blind, placebo-controlled trial, evaluated TCZ effectiveness in achieving sustained, corticosteroid -free remission. This was the first trial to employ a blinded, variable-dose corticosteroid-tapering regimen [38]. The study concluded that TCZ was not only highly effective in maintaining disease remission induced by the combination of TCZ and prednisone, but also that IL-6R blockade has a pronounced steroid-sparing effect for patients [41]. The trial had 4 arms: 1) TCZ SC 162 mg weekly plus 6-month prednisone taper; 2) TCZ SC 162 mg every other week plus 6-month prednisone taper; 3) prednisone only at 6-month taper; and 4) prednisone only at 12-month taper. Remission was sustained in 56% of the patients treated with TCZ for 52 weeks in the weekly group and in 53% in the 'every other week' groups, as compared with 14% in the 6 months prednisone taper group and 18% in the 12 months prednisone taper group ($P<0.001$ for the comparisons of either TCZ treatment with prednisone only groups). Serious adverse events occurred in 15% of the patients in the group that received TCZ weekly, 14% of those in the group that received TCZ every other week, 22% in the prednisone 6-moth taper group, and 25% in the 12 months prednisone taper group. Anterior ischemic optic neuropathy developed in one patient in the group that received TCZ every other week [31].

Table **1** summarizes all agents used for steroid-sparing and the type of evidence available and recommendation for steroid-sparing in GCA.

Table 1. Agents used for steroid-sparing in GCA treatments.

Serial No.	Steroid Sparing Agent	Levels of Evidence	Recommendation as a Steroid-Sparing Agent in GCA
1	Methotrexate	IB	Second line agent
2	Mycophenolate	IIIC	Third line agent
3	Azathioprine	IIIC	Third line agent
4	Cyclophosphamide	IIIC	Third line agent
5	Anti-TNF agents	IB	Etanercept can be used as second-line agent for induction of remission for corticosteroid refractory GCA)

(Table 1) contd.....

Serial No.	Steroid Sparing Agent	Levels of Evidence	Recommendation as a Steroid-Sparing Agent in GCA
6	Abatacept (Selective T-cell co-stimulation modulator)	IB	Can be an option as Third-line but larger studies required
7	Tocilizumab (IL6R-antagonist)	IA	First line agent (most robust evidence available)

*Levels of evidence: I-Systematic review of all relevant RCT's or an n=1RCT, II-Randomised trial or observational study with dramatic effect, III-Non-randomised controlled cohort/follow up study(observational), IV- Case-series, case-control studies, or historically controlled studies, V- mechanism-based reasoning (expert opinion, based on physiology, animal or laboratory studies).

*Grades: A- consistent level I studies, B- Consistent level II or III studies or extrapolations from level I studies, C- level IV studies or extrapolations from level 2 or 3 studies, D- level V evidence or troubling inconsistent or inconclusive studies of any level.

CONCLUSION AND RECOMMENDATION

At the time of writing, there was no British Society for Rheumatology guidance although this may be revised soon. We analysed 13 studies (Table **2**). There were two studies that did not support the additive value of the use of steroid-sparing agents. Five studies concluded that due to their small sample size, they recommend conducting further larger studies and 11 studies concluded that there was significant value to the use of steroid-sparing agents in side-effect reduction and clinical outcomes improvement.

Considering all the evidence available for choosing the most appropriate steroid-sparing agent in GCA, a large number of studies favoured TCZ. There is good evidence that it can safely be used for:

- Steroid-sparing
- Induction of remission
- Maintenance of remission
- Less frequent flare-ups

The next best agent for steroid-sparing effect appears to be MTX. There is good quality evidence that supports the use of MTX to reduce flares in relapsing GCA and help in reducing the corticosteroid dose and adverse effects.

Amongst anti-TNF agents, use of etanercept can be an option in corticosteroid refractory GCA to induce remission. Abatacept, a selective T cell co-stimulation modulator had shown promise in reducing relapse in GCA in RCTs involving a small number of GCA patients.

Immunosuppressants like azathioprine, mycophenolate, and cyclophosphamide may be used in refractory GCA or large vessel vasculitis patients as third-line agents.

Table 2. List of studies included in the systematic review.

Citation	Sample	Type	Results (Direct Quotation)	Disagree with the value adding of steroid sparing agents	Agree with the value adding of steroid sparing agents	More research required
Z. Su, V. Menon, R. Gliklich, T. Brecht, "Treatment patterns in Large vessel vasculitis (Giant cell arteritis and Temporal arteritis): Findings from a large contemporaneous real world cohort in US", Arthritis and Rheumatology, vol 69, (suppl 10), 2017.	n=1,567 patient records	Medical records audit	*The cohort included 1,567 patients with a mean age of 72 + 10 years, three quarters were Caucasian (78%) and female (76%). Median follow up time was 24 months with a mean of 12 rheumatology ambulatory encounters. Nearly a third of the cohort had a concomitant diagnosis of polymyalgia rheumatica (33%) and 17% had rheumatoid arthritis. A majority of the patients had at least one erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurement. Median ESR at baseline was 21mm/hr (IQR: 8, 48) and median CRP was 1mg/L (0.3, 4.0). Only 6% of patients had a documented temporal artery biopsy. Patient reported pain scores were available in 26% of the patients with a median duration of 6 months between first and last assessment. The majority of patients received glucocorticoids (85%), 22% were treated with methotrexate, 8% with hydroxychloroquine, 5% with aspirin, 5% with tocilizumab and 3.5% with azathioprine; 14% were treated with more than one drug concurrently.*	✓		

(Table 2) contd.....

Citation	Sample	Type	Results (Direct Quotation)	Disagree with the value adding of steroid sparing agents	Agree with the value adding of steroid sparing agents	More research required
I. Kötter, J. C. Henes, A. D. Wagner, J. Loock, W. L. Gross, "Does glucocorticosteroid-resistant large-vessel vasculitis (giant cell arteritis and Takayasu arteritis) exist and how can remission be achieved? A critical review of the literature", Clinical and Experimental Rheumatology, vol 30 issue 1, Suppl 70, pp 114-129, 2012.	n=64 publications	Systematic review	*Sixty-four publications were found. Five case series described large cohorts of patients with GCA (n=2) or TA (n=3) showing that 40.8% to 48% of GCA patients and 46% to 84% of TA patients require additional immunosuppressive agents to achieve remission and taper GC. Most were on biologic agents (mainly infliximab, 24 publications/123 patients), followed by methotrexate (MTX) (14/113), cyclophosphamide (CYC) (9/27), azathioprine (AZA) (8/51), cyclosporine A (CSA) (6/47), mycophenolate mofetil (MMF) (3/32), leflunomide (LEF) (2/2), chlorambucil (1/1) and antimalarials (1/36). There were also 2 case reports on autologous stem cell transplantation. The distribution of the two entities TA and GCA was as follows: MTX: 98% GCA, 2% TA; IFX: 26.8% GCA, 73.2% TA; CYC: 70.4% GCA, 29.6% TA; AZA: 100% GCA; LEF: 100% TA; MMF: 100% TA; antimalarials: 100% GCA, autologous stem cell transplantation: 100% TA. A distinction between GC-resistant and GC-dependent cases could not be made from the data available. However, 50 (79%) of the publications described GC-resistant cases. Whereas almost all case reports and retrospective case series (with the exception of CSA) revealed steroid-sparing effects, the 3 prospective randomised trials and 2 open prospective controlled trials on MTX gave conflicting results. However, a recent meta-analysis which recalculated the original data resulted in superiority of MTX after 24 months, there were less relapses and lower GC doses in the MTX group. The prospective controlled IFX trial where IFX was randomised against placebo after GC-induced remission of GCA did not show advantages for IFX over GC alone for maintenance of remission. The prospective controlled ETA trial, which comprised 17 GCA patients, showed small, non-significant advantages but was too small to draw definite conclusions.*			✓
G. S. Hoffman, M. C. Cid, D. B. Hellmann, et al., "International Network for the Study of Systemic Vasculitides, A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis", Arthritis and Rheumatology, vol 46, pp 1309-1318, 2002.	n=98 patients	RCT	*Ninety□eight patients were enrolled. No significant differences between treatment groups were noted with regard to age, frequency of positive findings on temporal artery biopsy (placebo 87%, MTX 79%), or comorbidities at the time of enrollment. The median dosage of MTX was 15 mg/week. The incidence of treatment failure was comparable between groups after 12 months: 57.5% in the MTX group failed treatment (95% confidence interval [95% CI] 41.6–73.4%) compared with 77.3% in the placebo group (95% CI 61.9–92.8%) (P = 0.26). In a Cox regression analysis, MTX was not associated with a reduced risk of treatment failure (relative risk 0.72; 95% CI 0.41–1.28). There were no significant differences between groups with regard to abnormal elevations of the erythrocyte sedimentation rate following initial remissions, serious morbidity due to GCA, cumulative CS dose, or treatment toxicity. In the MTX group, there were fewer cases of GCA relapse heralded by symptoms of isolated polymyalgia rheumatica (1 case versus 5 in the placebo group; P = 0.05).*		✓	

(Table 2) contd.....

Citation	Sample	Type	Results (Direct Quotation)	Disagree with the value adding of steroid sparing agents	Agree with the value adding of steroid sparing agents	More research required
J. A. Jover, C. Hernandez-Garcia, I. C. Morado, et al., "Combined treatment of giant-cell arteritis with methotrexate and prednisone. A randomized, double-blind, placebo-controlled trial", Annals of Internal Medicine, vol 134, pp 106-114, 2001.	n+21 patients	RCT	*Twenty-one patients received prednisone and methotrexate and 21 received prednisone and placebo. The 2 groups were similar at baseline, with a mean age of 78 years, a mean erythrocyte sedimentation rate of 91 and 100 mm/h respectively, and a polymyalgia rheumatica prevalence of 57% and 52% respectively. One patient in the methotrexate group and 2 in the placebo group were lost to follow-up. All patients responded to initial treatment. Disease relapse occurred in 9 patients (45%) in the methotrexate group, compared with 16 patients (84%) in the placebo group (p = 0.018). Moreover, fewer relapses involving cranial symptoms occurred among patients in the methotrexate group than among the control subjects (2 v. 7 patients, p = 0.06). The median duration of prednisone treatment was significantly shorter in the methotrexate group than in the placebo group (29 v. 94 weeks, p = 0.0016), resulting in a lower mean cumulative dose of prednisone (4187 v. 5489 mg, p = 0.009). There was a trend toward a lower incidence of diabetes mellitus (3 v. 7 patients), arterial hypertension (12 v. 16 patients) and cushingoid appearance (3 v. 6 patients) in the methotrexate group. Three patients receiving methotrexate experienced myelosuppression or mucositis that necessitated withdrawal of the drug. Of these, 1 patient was not taking folic acid supplementation and 2 had mild renal impairment*		✓	✓
R. F. Spiera, H. J. Mitnick, M. Kupersmith, et al., "A prospective, double-blind, randomized, placebo-controlled trial of methotrexate in the treatment of giant cell arteritis (GCA)", Clinical and Experimental Rheumatology, vol 19, pp 495-501, 2001.	n=21 patients	RCT	*Twenty-one patients were enrolled, 12 randomized to methotrexate, 9 to placebo. Baseline characteristics (age, height, weight, sedimentation rate, bone mineral density, total corticosteroid dose prior to randomization, and quality of life as measured by SF-36 and function as measured by AIMS) were comparable between groups.*	✓	✓	
			At completion, there was no significant difference between methotrexate-and placebo-treated patients with regard to the cumulative corticosteroid dose (6469 mg and 5908 mg respectively, p=0.6), number of weeks to completion of steroids (68 and 60 respectively, p=0.5), time (weeks) to taper prednisone to less than 10 mg prednisone/day (23 and 25 respectively, p=0.5), bone mineral density in lumbar spine (p=0.2) or hip (p=0.4) at one year, or functional status as measured by AIMS and quality of life as measured by SF36. There was no late vision loss in either group, and only one major treatment-responsive relapse in a methotrexate-treated patient. There were few major corticosteroid-related side effects and these did not significantly differ between groups.	✓	✓	

(Table 2) contd.....

Citation	Sample	Type	Results (Direct Quotation)	Disagree with the value adding of steroid sparing agents	Agree with the value adding of steroid sparing agents	More research required
A. D. Mahr, J. A. Jover, R. F. Spiera, et al., "Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis", Arthritis and Rheumatology, vol 56, pp2789-27, 2007.	n=161 patient records	Medical records audit	*The combined data set comprised 161 patients, of whom 84 received MTX and 77 received placebo. The mean duration of follow-up was 54.7 weeks (SD 39.2 weeks). Hazard ratios (HRs) for a first and second relapse of GCA were 0.65 (P = 0.04) and 0.49 (P = 0.02), respectively, in patients receiving MTX as compared with patients receiving placebo. Accordingly, a predicted 3.6 individuals (95% confidence interval [95% CI] 2.2–56.8) and 4.7 individuals (95% CI 3.3–21.9) need to be treated with MTX to prevent the occurrence of one first or one second relapse, respectively, up to 48 weeks. Use of MTX resulted in a reduction in the corticosteroid cumulative dose by 842 mg within 48 weeks (P < 0.001). Moreover, MTX treatment was associated with a higher probability of achieving sustained discontinuation of corticosteroids for ≥24 weeks (HR 2.84, P = 0.001). Dropout rates and occurrence of adverse events did not differ between treatment groups.*		✓	
F. Buttgereit, C. Dejaco, E. L. Matteson, B. Dasgupta, "Polymyalgia rheumatica and giant cell arteritis: a systematic review". Journal of American Medical Association, vol 315, pp 2442-2458, 2016.	n=20 RCT (therapy, n = 1016 patients) and n=30 (imaging, n = 2080 patients)	Systematic review	*Twenty randomized clinical trials for therapy (n = 1016 participants) and 30 imaging studies for diagnosis and/or assessing response to therapy (n = 2080 participants) were included. The diagnosis of PMR is based on clinical features such as new-onset bilateral shoulder pain, including subdeltoid bursitis, muscle or joint stiffness, and functional impairment. Headache and visual disturbances including loss of vision are characteristic of GCA. Constitutional symptoms and elevated inflammatory markers (>90%) are common in both diseases. Ultrasound imaging enables detection of bilateral subdeltoid bursitis in 69%of PMR patients. In GCA, temporal artery biopsy remains the standard for definitive diagnosis. Ultrasound and magnetic resonance imaging (MRI) of large vessels revealing inflammation-induced wall thickening support the diagnosis of GCA (specificity 78%-100% for ultrasound and 73%-97%for MRI). Glucocorticoids remain the primary treatment, but the optimal initial dose and tapering treatment regimens are unknown. According to consensus-based recommendations, initial therapy for PMR is prednisone, 12.5 to 25mg/day or equivalent, and 40 to 60mg/day for GCA, followed by individualized tapering regimens in both diseases.*		✓	
			Adjunctive methotrexate may reduce cumulative glucocorticoid dosage by 20%to 44%and relapses by 36%to 54%in both PMR and GCA. Use of tocilizumab as additional treatment with prednisone showed a 2-to 4-fold increase in remission rates of GCA in a randomized clinical trial (N = 30).		✓	

(Table 2) contd.....

Citation	Sample	Type	Results (Direct Quotation)	Disagree with the value adding of steroid sparing agents	Agree with the value adding of steroid sparing agents	More research required
R. Smith, K. P. Kuet, R. Kilding, M. Akil, J.Maxwell., "A comparison of the effectiveness of mycophenolate mofetil or methotrexate in combination with prednisolone versus prednisolone alone in the treatment of large vessel vasculitis", Annals of the Rheumatic Diseases, vol 77, pp 1490, 2017.	n=65 patients	Cohort comparative study	*65 patients were included in the study, 41 with GCA and 24 LVV. 49 were female and 16 male. Mean age at diagnosis was 68; range 21 to 87. 37 patients were treated with prednisolone alone; 35 had GCA and 2 LVV. 20 were treated with MMF and prednisolone; 4 with GCA and 16 LVV. 8 were treated with MTX and prednisolone; 2 had GCA and 6 LVV. The AOC for prednisolone and CRP were not normally distributed across the cohort, and non-parametric methods were therefore used for comparisons. Median AOC prednisolone dose for the prednisolone only group was 68.0, (interquartile range (IQR) 17.7, n=37), for the MMF treated group 70.8 (IQR 28.7, n=20) and for the MTX treated group 67.8 (IQR 20.4 n=8). Median AOC CRP was highest in the group treated with prednisolone alone (58.9, IQR 34.5) compared to MMF (43.8, IQR 26.5) and MTX (49.3 IQR 67.5) but there were no statistical differences between median AOC prednisolone dose or CRP in either the unadjusted or regression models.*		✓	✓
S. Sciascia, D. Piras, S Baldovino, et al.,, "Mycophenolate mofetil as steroid sparing treatment for elderly patients with giant cell arteritis: Report of three cases", Aging Clinical and Experimental Research, vol 24, issue 3, pp 273-277, 2012.	n=3 patients	Case presentation	*All three patients showed clinical benefit, and were also able to taper steroid use to a more rapid regimen compared with the recently suggested steroid reduction approach. MMF was well tolerated, and no signs of toxicity were observed in a mean of 21.6 months (12-29) of follow- up*		✓	
A. S. Boureau, P. de Faucal, O. Espitia, L. De Decker, C. Agard, "Place of azathioprine in the treatment of giant cell arteritis", Revue de Medecine Interne, vol 37, issue 11, pp 723-729, 2016.	n=28 patient medical records	Medical records audit	*Of the 28 patients included, 21 responded to azathioprine. At 1 year of follow-up after the initiation of azathioprine, 18 patients (64%) were still in sustained response, asymptomatic, without increase in acute phase response laboratory markers, and with a daily dose of prednisone<10 mg. Three patients (11%) experienced a relapse during azathioprine treatment. Mean daily dose of prednisone were 25.4 mg at the time of initiation of azathioprine, and 4.7 mg at 1 year of treatment, suggesting a corticosteroid-sparing effect (P<0.001). Ten patients experienced azathioprine serious side effects, leading to discontinuation of treatment in seven cases.*		✓	
L. Quartuccio, M. Maset, G. De maglio, et al., "Role of oral cyclophosphamide in the treatment of giant cell arteritis", Rheumatology, vol 51, issue 9, pp 1677-1686, 2012.	n=19 patient medical records	Medical records audit	*The efficacy of CYC was observed in 15 of the 19 patients, and remission was still present 6-12 months after CYC suspension in 12 of the 13 patients. GCs were suspended in 6 of the 15 patients, and they were continued at a dose ≤ 5 mg/day of prednisone in all the remaining responders. Relapse occurred in 4 of the 15 patients, usually >12 months after CYC suspension. Suspension of GC daily dose or reduction to ≤ 5 mg/day of prednisone occurred within the first 6 months of follow-up after the beginning of CYC in 10 of the 15 patients. Ten adverse events were registered in nine patients, with recovery usually soon after the suspension of CYC or dose reduction.*		✓	
			However, one death occurred due to acute hepatitis. Disappearance of the inflammatory infiltrate could be demonstrated when temporal artery biopsy was repeated 3 months after CYC in one patient.		✓	

(Table 2) contd.....

Citation	Sample	Type	Results (Direct Quotation)	Disagree with the value adding of steroid sparing agents	Agree with the value adding of steroid sparing agents	More research required
L. Silva, E. Loza, V. M. Martínez-Taboada, et al., "Biological therapy for large vessel vasculitis: A systematic review", Seminars in Arthritis and Rheumatism, vol 43, issue 4, pp 542-557, 2014.	n= 90 studies	Systematic review	*Of 3447 citations, abstracts, and hand-searched studies screened, 90 were included. Most of the studies included ANCA-associated vasculitis (AAV) patients and only a few included large vessel vasculitis (LVV) patients. Rituximab was the most used agent, having demonstrated efficacy for remission induction in patients with AAV. A number of studies used different anti-TNFα agents with contrasting results. A few uncontrolled studies on the use of abatacept, alemtuzumab, mepolizumab, and tocilizumab were found.*		✓	
S. H. Unizony, B. Keroack, J. H. Stone, "Tocilizumab for the treatment of giant cell arteritis: Extended follow-up", Presse Medicale, vol 42, pp 727, 2013.	n=12 patients	Case presentation	*The mean follow-up of this cohort since diagnosis was 37 months (range 17–70). Eight subjects had failed at least one immunosuppressant (methotrexate, azathioprine, cyclophosphamide, infliximab, adalimumab and etanercept), and four had contraindications for the use of GC. TCZ (4mg/kg, n =3 and 8mg/kg, n =9) was given for a mean period of 16 months (range 6–27). Before and during IL-6R blockade, the patients experienced an average of 2.7 (95% CI 2–3.5) and 0.6 (95% CI 0–1.2) disease exacerbations per year, respectively (P =0.0006). The mean daily prednisone dose of the cohort decreased from 24mg (95% CI 15–33.5) at the time of TCZ initiation to 7.3mg (95% CI 0.7–14) by the time of last evaluation (P =0.01). On TCZ, 7 subjects maintained disease remission until the end of follow-up for a mean time of 17.5 months (range 8–26), and 5 patients flared after an average of 11 months of therapy (range 2–25). The mean prednisone dose at the time of disease flare in these 5 patients was 4.5mg/day. One subject relapsed after TCZ discontinuation. Currently, 5 patients take 5mg/day of prednisone or less, and 3 patients are off GC. Adverse effects attributable in part to TCZ in this series included leucopenia (n =5), transaminitis (n =8), and pneumonia (n =1). Autopsy on one patient who died from an unrelated cause revealed persistent vasculitis.*			✓
J. H. Stone, K. Tuckwell, S. Dimonaco S et al., "Trial of tocilizumab in giant-cell arteritis", The New England Journal of Medicine, vol 377, pp 317–328, 2017.	n=251 patients	RCT	*Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab weekly and in 53% of those treated with tocilizumab every other week, as compared with 14% of those in the placebo group that underwent the 26-week prednisone taper and 18% of those in the placebo group that underwent the 52-week prednisone taper (P<0.001 for the comparisons of either active treatment with placebo). The cumulative median prednisone dose over the 52-week period was 1862 mg in each tocilizumab group, as compared with 3296 mg in the placebo group that underwent the 26-week taper (P<0.001 for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper (P<0.001 for both comparisons). Serious adverse events occurred in 15% of the patients in the group that received tocilizumab weekly, 14% of those in the group*		✓	✓

(Table 2) contd.....

Citation	Sample	Type	Results (Direct Quotation)	Disagree with the value adding of steroid sparing agents	Agree with the value adding of steroid sparing agents	More research required
			that received tocilizumab every other week, 22% of those in the placebo group that underwent the 26-week taper, and 25% of those in the placebo group that underwent the 52-week taper. Anterior ischemic optic neuropathy developed in one patient in the group that received tocilizumab every other week.		✓	✓

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICTS OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Decleared none.

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