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

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ABSTRACT
Introduction. The mainstay in the treatment of the large-vessel vasculitides giant cell arteritis (GCA) and Takayasu arteritis (TA) are glucocorticosteroids (GC) for induction of remission as well as for its maintenance in low doses for 1 to 2 years. However, clinical practice includes GC-resistant cases without sufficient response to standard GC for induction of remission and GC-dependent cases where a dose reduction of GC without relapse is impossible after successful induction of remission. The aim of this study was to evaluate the data on treatment options in these situations.

Materials and methods. A literature search in PubMed matching the terms giant cell arteritis and Takayasu arteritis with all possible immunosuppressive and biological agents as well as with the terms “treatment, therapy and management” was performed.

Results. 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.

Conclusion. Although GCA is the commonest systemic vasculitis, prospective randomised trials on steroid sparing agents are rare and mostly included only small patient numbers. Inclusion and response criteria were heterogeneous, and observation periods and follow-up were often short. Criteria for GC-resistance or GC-dependence and for disease remission have not been uniformly defined. There is still an urgent need for prospective randomised trials with larger patient groups, longer follow-up and well defined inclusion criteria and criteria for response and remission.

Competing interests: none declared.
relapse, using standardised disease activity scoring systems, in order to be able to give evidence-based recommendations for patients not responding to GC alone in the future.

Introduction

Primary large-vessel vasculitides by definition affect the aorta and its branches and include giant cell arteritis (GCA) and Takayasu arteritis (TA). These are distinct disorders with different ages of onset and ethnic distributions as well as HLA associations. However, histopathology is similar; a granulomatous vasculitis with giant cells (1). There are distinct ACR classification criteria for both disorders (2-4). More recently, EULAR recommendations for the management of large-vessel vasculitides have been published (5). Early initiation of high-dose GC therapy (1 mg/kg body-weight (bw/day) for induction of remission is recommended. The experts also recommend that an immunosuppressive agent should be considered as adjunctive therapy. In the more detailed description, it is stated that methotrexate may be used in GCA, azathioprine (AZA) in TA, and also cyclophosphamide may be effective in glucocorticosteroid (GC) resistant TA. Infliximab (IFX) is said not to be effective as far as relapse rate is concerned and hence is not recommended. The authors recommend the use of low-dose aspirin in all patients with GCA because of an increased risk of cardiovascular and cerebrovascular events.

Obviously, as some of the articles (pp. S70, S130) in this issue of Clin Exp Rheumatol show, when treated exclusively with GC, a considerable number of patients do not achieve remission of disease activity – which would be called GC-resistance – or GC cannot be reduced below 7.5 mg prednisolone equivalent in a justifiable amount of time without relapse. The latter would be called GC-dependence. Higher doses of GC (more than 10 mg prednisolone equivalent) over a longer period of time (more than 6 months) are associated with a high risk of adverse effects, which have been well documented in patients with GCA/TA. Up to 86% of GCA patients have been affected by GC-related side effects (6-8). Long-term GC use appears to be associated with an increased risk of severe and opportunistic infections (6), and an increased mortality rate within the first months of initial high dose GC treatment as well as with daily maintenance doses over 10 mg prednisolone equivalent has been described (6, 9-11). Furthermore, there appears to be a subclinical disease activity with an incidence of large artery stenosis and aortic aneurysms or dissections of about 25% during follow-up, and active aortitis was demonstrated in the majority of cases of fatal aortic dissection (12-16).

Hence, steroid-sparing treatment and agents with potent remission-inducing capabilities may be needed.

Methods


The articles found were read thoroughly, classified by type (prospective trial, randomised, non-randomised, controlled, uncontrolled, case series, case reports) and disease (GCA or TA), and evaluated for dosages used and responses achieved, as well as for previous treatments the patients had been resistant to.

Results

Sixty-four articles were found (Table I), 14 for MTX (1-98 patients), including 5 randomised trials and 2 prospective open-label studies (17-30), 8 for AZA (1-10 patients), including one prospective placebo-controlled trial and one prospective trial prematurely stopped due to suspected adverse events (AE) and inefficacy (24, 31-39), 6 publications for cyclosporine A (CSA) (1 to 60 patients, including one prospective randomised open trial) (40-45), 2 case reports for lefunomide (LEF) (46, 47), 3 case series for mycophenolate mofetil (MMF) (3 to 21 patients) (48-50), 9 for cyclophosphamide (CYC) (1 to 10 patients) (51-59). One single publication was a retrospective case series on anti-malarials (hydroxychloroquine, HCQ) as primary steroid-sparing agent, which did not add efficacy (60), overall recovery rate was 58%. Thirty-five articles with 1 to 44 patients described the efficacy of biologic agents, among these none was found for the newer TNF antagonists golimumab and certolizumab and for abatacept. There were 24 publications for infliximab including 1 to 44 patients, including 2 prospective multicentre trials (61-84). Some of the case series described a switch to etanercept (ETA) or adalimumab (ADA), mostly for convenience reasons and not because of inefficacy (65, 70). 3 publications (85, 86) including one prospective trial focused on ETA (17 patients, prospective, double-blind placebo-controlled single centre study) (87), 2 on ADA (case reports) (88, 89), 5 on tocilizumab (TCZ) (1 to 7 patients) (90-94), 3 on rituximab (RTX) (1 to 3 patients) (95-97). In addition, the keywords “management, treatment and therapy” revealed additional literature on the use of chlorambucil (one case report) (98), antimalarials (60), and autologous stem cell transplantation (two cases, one single case of treatment resistant TA described in a case series on vasculitis and in a registry-based analysis) (99-101).

Most of the case series and case reports, especially when biological agents were used, were conducted in patients with TA, whereas the prospective trials almost exclusively included patients with GCA.

Most of the case reports and case series described positive outcomes of the respective rescue/steroid sparing treatment. There were a few exceptions providing negative results or describing the development of newly onset GCA or TA under immunosuppressive treatment for comorbidities such as Crohn’s disease (77). In detail, two publications report inefficacy of CYC in 2 patients with TA (51, 56), in the second case report by Simon et al., the patient later died.
## Early data for non-biologic agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Previous treatments</th>
<th>Dosage</th>
<th>Observation period</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Case series</td>
<td>3, 2 with GCA</td>
<td>PMR/GCA resistant</td>
<td>7.5-12.5 mg/week orally</td>
<td>7-22 weeks</td>
<td>Remission, GC reduced, steroid sparing</td>
</tr>
</tbody>
</table>

### Years and Authors

1. **1989**
   - **Krall PL, Mazanec DJ, Wilke WS:** Cleveland Clin J Med 1989;56:253-7 (17)
   - **Feinberg HL et al.**, J Rheumatol (and PMR) 1996; 23:1550-52 (20)
   - **Shetty et al.**, Clin Exp Rheumatol 1998; 16:335-336 (22)
   - **Kupersmith et al.**, Br J Ophthalmol 1999; 83:796-801 (23)
   - **Spiera et al.**, Clin Exp Rheumatol 2001; 19:495-501 (26)
   - **Jover et al.**, Ann Intern Med 2001; 144:1091-114 (27)
   - **Besson-Léaud et al.**, Archives de Pediatrie 2001; 8:724-727 (24)
   - **Rimar et al.**, J Rheumatol 2006; 33:1458-1459 (29)
   - **Camellino et al.**, Clin Exp Rheumatol 2010; 28:258-262 (28)
   - **Montoya S, Schweizer Med Woch 1969; 99:1022 (33)

### Year 1989: Use of Methotrexate in PMR and GCA

- **Krall PL, Mazanec DJ, Wilke WS:** Cleveland Clin J Med 1989;56:253-7 (17)
  - Methotrexate 10 mg/week orally. PMR/GCA Case series. 3, 2 with GCA. PRED resistant, dose reduction of PRED possible. Not given. 7 weeks to 22 months. Remission, GC reduced, steroid sparing.

### Year 1994: Use of Methotrexate in GCA

  - Methotrexate 10 mg/week orally. GCA Prospective open. 11 patients. 10 mg/week orally. Observation period: 22-37 months. 10 patients discontinued GC, MTX safe and steroid sparing.

### Year 1994: Use of Methotrexate in GCA

  - Methotrexate 7.5 mg/week orally. GCA Case reports. 3, 1 MTX, 1 Prednisolone. Not given. Observation period: Patient died due to septicemia.

### Year 1994: Use of Methotrexate in PMR

- **Feinberg HL et al.**, J Rheumatol (and PMR) 1996; 23:1550-52 (20)
  - Methotrexate 7.5 mg/week orally. PMR with GCA, Prednisolone, inadequately controlled. Observation period: 9 months. No steroid sparing effect in PMR.

### Year 1996: Use of Methotrexate in GCA

  - Methotrexate 7.5 mg/week orally. GCA Randomised, double-blind. 6 patients. Active untreated MTX as first line treatment. Observation period: 21 weeks. Pred PRED reduced by 50%, median duration pred 47.5 weeks. No steroid sparing effect compared to PBO.

### Year 1996: Use of Methotrexate in TA

- **Shetty et al.**, Clin Exp Rheumatol 1998; 16:335-336 (22)
  - Methotrexate 2 mg/kg. TA Case report. 1 child, A 6-year-old Trench TA. Pred only partially effective. Observation period: 12 months. Steroid sparing and remission achieved.

### Year 2001: Use of Methotrexate in GCA

- **Kupersmith et al.**, Br J Ophthalmol 1999; 83:796-801 (23)
  - Methotrexate 10 mg/week orally. GCA Prospective, randomised. 22 patients with newly diagnosed severe GCA. Observation period: 12 months. High-dose GC can be given to elderly patients. Without contraindication, MTX not steroid sparing in this setting.

### Year 2001: Use of Methotrexate in GCA

- **Spiera et al.**, Clin Exp Rheumatol 2001; 19:495-501 (26)
  - Methotrexate 40-900 mg MTX initially. GCA Prospective, double-blind, PBO controlled. 34 patients. Newly-diagnosed active GCA. Observation period: 24 months. No steroid sparing effect of MTX, no difference in AE.

### Year 2001: Use of Methotrexate in GCA

- **Jover et al.**, Ann Intern Med 2001; 144:1091-114 (27)
  - Methotrexate 10 mg/week orally. GCA Double-blind, PBO-controlled. 34 patients. Newly-onset active, treated in combination with PRED 60 mg/day p.o. Initially. Observations 24 months. Reduction of no of relapses in MTX group. No difference compared to PBO group. Siginificantly less cumulative GC in MTX group. No difference in AE.

### Year 2002: Use of Methotrexate in GCA

  - Methotrexate 30-1000 mg after clinical judgement. GCA Multicentre, PBO-controlled. 42 patients. Newly-onset active. All treated with PRED 15mg/week p.o. Observation period: 12 months. No reduction of risk of treatment failure by MTX, no differences for complications, may improve final VA.

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  - Methotrexate 40-900 mg MTX initially. GCA Prospective, double-blind, PBO controlled. 34 patients. Newly-diagnosed active GCA. Observation period: 24 months. Reduction of no of relapses in MTX group. No difference in AE.

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### Year 2006: Use of Methotrexate in GCA

- **Besson-Léaud et al.**, Archives de Pediatrie 2001; 8:724-727 (24)
  - Methotrexate 100 mg/day, PRED 1. GCA (AT) Case report. 1 child with TA. Pred only partially effective. Observation period: 12 months. Steroid sparing and remission achieved.

### Year 2006: Use of Methotrexate in GCA

  - Methotrexate 200 mg/day, PRED 1. GCA (AT) Case report. Among 1 Primary treatment in combination with PRED 10 mg/day. Observation period: 12 months. Effective.

### Year 2006: Use of Methotrexate in GCA

- **Rimar et al.**, J Rheumatol 2006; 33:1458-1459 (29)
  - Methotrexate 100 mg/kg. GCA Case series. 15, 6 treated with AZA. Reason for AZA: complications. Observation period: 12 months. PRED reduction possible after addition of AZA.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Type of large-vessel vasculitis</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Previous treatments</th>
<th>Dosage</th>
<th>Observation period</th>
<th>Response</th>
<th>Year</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCA (AT)</td>
<td>Case series</td>
<td>2</td>
<td>80 mg fluocortolone, ineffective in 1, AE in 1</td>
<td>150 mg/day</td>
<td>6-12 months</td>
<td>AZA steroid sparing</td>
<td>1975</td>
<td>Wenig und Meiser, Nervenarzt 1975; 46:453-457 (33)</td>
<td></td>
</tr>
<tr>
<td>GCA (AT)</td>
<td>Case series, retrospective</td>
<td>10, 5 with biopsy-proven AT in addition to PMR</td>
<td>150 mg/day orally</td>
<td>6 months</td>
<td>Relapses in 9 after discontinuation of PRED, AZA not steroid sparing</td>
<td>1977</td>
<td>Loe scholl et al., Ugeskr Laeg. 1977;139:26-18-2620 (34)</td>
<td></td>
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<tr>
<td>GCA</td>
<td>Prospective, double-blind, PRD controlled, single centre</td>
<td>31, not differentiated between GCA/PRD or overlap</td>
<td>1.5-2.7 mg/kg orally/day</td>
<td>52 weeks</td>
<td>PRED reduction more prominent in AAZA group, significant at week 52</td>
<td>1986</td>
<td>De Silvia et al., Ann Rheum Dis 1986; 45:138-138 (35)</td>
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<td></td>
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<tr>
<td>GCA (AT)</td>
<td>Prospective, randomised PRED alone vs. AAZA plus PRED, single centre</td>
<td>12</td>
<td>2/7 jaundice under AAZA, ineffective in 3/5of the following patients - patient number not precisely provided, brief letter</td>
<td>100–150 mg/day</td>
<td>Planned: 12-18 months</td>
<td>Stopped prematurely due to AE and inefficacy of AAZA</td>
<td>1995</td>
<td>Gonzalez-Gay et al., 1995; Rev Rheum Ed Francaise 62:568 (36)</td>
<td></td>
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<tr>
<td>GCA</td>
<td>Case report</td>
<td>Gential tract, AT</td>
<td>Primarily PRED plus AAZA</td>
<td>100 mg, in parallel PRED augmented to 3 x 1 g iv.</td>
<td>5 months</td>
<td>Remission, PRED tapered</td>
<td>1996</td>
<td>Inanc et al., J Rheumatol 1996; 23:393-393 (37)</td>
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<tr>
<td>GCA (TA)</td>
<td>Case report</td>
<td>Gential tract, AT</td>
<td>AAZA resistance (60 mg)</td>
<td>100 mg</td>
<td>3 months</td>
<td>Improvement, GC weaned</td>
<td>2009</td>
<td>Papahadjis et al., Eur J Ophthalmol 2009; 19:868-869 (38)</td>
<td></td>
</tr>
<tr>
<td>Antimalarials</td>
<td>GCA Retrospective case series</td>
<td>36</td>
<td>18 primary add. GC, 15 secondary after unability to reduce GC (dependence)</td>
<td>HCQ 400 mg/day</td>
<td>5 ys (mean)</td>
<td>Recovery rate 58%</td>
<td>1994</td>
<td>Le Guesne et al., Rev Rheum Ed Fr 1994; 6:485-490 (60)</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>GCA, TA Case reports</td>
<td>2 (1 GCA, 1 TA)</td>
<td>Resistant to PRED 100 mg/day</td>
<td>100 mg/ml serum level</td>
<td>Not given</td>
<td>PRED reduction possible, remission and control of symptoms</td>
<td>1985</td>
<td>Wendling et al., Arthr Rheum 1985; 28:1078-1079 (40)</td>
<td></td>
</tr>
<tr>
<td>TA Case report</td>
<td>1</td>
<td>Resistant to PRED 100 mg/day</td>
<td>130 mg/ml serum level</td>
<td>Not given</td>
<td>PRED reduction possible, remission and control of symptoms</td>
<td>1992</td>
<td>Perez Garcia et al., Revista Clinica Espanola 1992; 190:470-471 (41)</td>
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<tr>
<td>GCA Randomised, controlled single centre</td>
<td>22</td>
<td>GCA with impossibility of tapering PRED</td>
<td>2mg/kg bw</td>
<td>6 months</td>
<td>No difference between groups</td>
<td>1998</td>
<td>Schaufelberger et al., Br J Rheumatol 1998; 37:464-465 (42)</td>
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<tr>
<td>TA Case report</td>
<td>1 child 13 ys</td>
<td>Active disease in spite of 0.5 mg/kg PRED</td>
<td>70-100 mg/ml serum level</td>
<td>4 ys</td>
<td>Remission, reduction of PRED level</td>
<td>1999</td>
<td>Horigome et al., MJA 1999; 170: 566-569 (43)</td>
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<tr>
<td>GCA Prospective randomised open multicentre trial, Control: PRED alone</td>
<td>60</td>
<td>Newly diagnosed, previously untreated</td>
<td>2.18mg/kg (mean)</td>
<td>12 months</td>
<td>No difference between the 2 groups, higher rate of AE in CSA group</td>
<td>2006</td>
<td>Schaufelberger et al., J Rheumatol 2006; 35: 327-329 (44)</td>
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<tr>
<td>GCA (AT)</td>
<td>Case report</td>
<td>Gential tract, AT</td>
<td>Newly diagnosed, severe tongue necrosis</td>
<td>100 mg</td>
<td>3 months</td>
<td>Remission</td>
<td>2007</td>
<td>Schutz Maas et al., Braz J Otorhinolaryngol 2007;53:717 (45)</td>
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<tr>
<td>Leflunomide</td>
<td>TA Case report</td>
<td>1</td>
<td>Resistant to PRED and MTX</td>
<td>20 mg/day</td>
<td>6 months</td>
<td>Remission, PRED tapered, slow response</td>
<td>2001</td>
<td>Haberhauser et al., Clin Exp Rheumatol 2001; 19:477-478 (46)</td>
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<tr>
<td>Mycophenolic acid/TA</td>
<td>Case series, retrospective</td>
<td>3</td>
<td>Dependent on high doses of PRED, 2 pre-treated with CYC, CSA, MMF</td>
<td>MMF 2000mg/day</td>
<td>11-15 months</td>
<td>Remission and reduction of PRED in all</td>
<td>1999</td>
<td>Daina et al., Hypertension in Pregnancy 2008; 27:247-252 (47)</td>
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<tr>
<td>Mycophenolate Mofetil</td>
<td>TA Case series, retrospective</td>
<td>13, 10 evaluated</td>
<td>Persistent disease activity despite PRED and/or other immunosuppressive drug or reactivation under PRED reduction or unacceptable PRED AE. 50% pre-treated with other immunosuppressives</td>
<td>MMF 2000mg/day</td>
<td>23.3 months (mean)</td>
<td>Significant decrease in PRED dose and reduction of disease activity in all</td>
<td>2007</td>
<td>Sinjai et al., Clin Rheumatol 2007;26:1871-1875 (49)</td>
<td></td>
</tr>
<tr>
<td>TA Case series, retrospective</td>
<td>21</td>
<td>55 % MMF as initial treatment, rest had AAZA before</td>
<td>MMF dosage not given</td>
<td>9.6 months (mean)</td>
<td>Significant decrease in disease activity as measured by ITAS (Indian Takayasu Arteritis activity score), only 2 MMF AE. Significant decrease in steroid dosage</td>
<td>2010</td>
<td>Goel et al., Clin Rheumatol 2010; 29:329-332 (50)</td>
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<td>Cyclophosphamide</td>
<td>TA Case report</td>
<td>1</td>
<td>PRED ineffective</td>
<td>1 mg/kg/day orally</td>
<td>4 months</td>
<td>Ineffective</td>
<td>1985</td>
<td>Jimenez-Akonso et al., Drug Intelligence and Clin Pharmacy 1985; 19:477 (51)</td>
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<tr>
<td>Medication</td>
<td>Type of study</td>
<td>Number of patients</td>
<td>Previous treatments</td>
<td>Dosage</td>
<td>Observation period</td>
<td>Response</td>
<td>Year</td>
<td>Authors</td>
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<tr>
<td>GCA</td>
<td>Case series, retrospective</td>
<td>4</td>
<td>Severe complications in spite of high dose PRED (1mg/kg bw/day)</td>
<td>0.5-1mg/kg bw orally/day</td>
<td>6-15 months</td>
<td>No severe AE, good control, in 2 patients treatment completely discontinued in remission after 2-3ys stabilized (2) or remission (2), PRED tapered. Rapid response in responders. Stabilisation, PRED reduced</td>
<td>1986</td>
<td>Pena Sanchez de Rivera et al., Medicine Clinica 1986; 86:306 (52)</td>
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<tr>
<td>GCA</td>
<td>Case series retrospective</td>
<td>4</td>
<td>Resistant to 6-MP</td>
<td>CYC pulses i.v., 0.5 to 1 g, total of 3 g in 3 weeks, CYC 75 mg orally/day</td>
<td>10-21 months</td>
<td>Not given</td>
<td>Improvement of visual acuity</td>
<td>1992</td>
<td>De Vita et al., J Intern Med 1992; 232:373-375 (53)</td>
</tr>
<tr>
<td>GCA(AT)</td>
<td>Case series, retrospective (1 with CYC)</td>
<td>4</td>
<td>With severe cerebral manifestations resistant to PRED</td>
<td>CYC (FAUCI) orally, 12.5 mg/m²/week orally, CYC 1.5-1.7 mg/kg orally/day</td>
<td>10 months</td>
<td>CYC ineffective, patient died later under ETA due to Candida sepsis No SAE, all responded and were in remission</td>
<td>1994</td>
<td>Bütter et al., Eur Neurol 1994; 34:162-167 (54)</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>Case report</td>
<td>1</td>
<td>Ocular TA resistant to PRED</td>
<td>Monthly iv CYC pulses 200 mg/m² x 10 150 mg/day orally</td>
<td>2 months</td>
<td>Improvement of VA (loss of vision was reversible)</td>
<td>2002</td>
<td>Rodriguez Hurtado et al., Eur J Med Res 2002; 7:128-130 (55)</td>
<td></td>
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<tr>
<td>TA</td>
<td>Case report</td>
<td>1</td>
<td>Ocular AT with normal ESR, steroid dependent, reduction or PRED under 10 mg impossible</td>
<td>Stabilised (2) or remission (2), PRED 1992</td>
<td>Discontinued in remission after 2-3ys</td>
<td>Medicina Clinica 1986; 86:306 (52)</td>
<td></td>
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<tr>
<td>TA</td>
<td>Case report</td>
<td>1</td>
<td>With mesenteric arteritis resistant to PRED, reduce or impossible, newly diagnosed TA</td>
<td>MTX, 12.5 mg/m²/week orally, CYC 1.5-1.7 mg/kg orally/day</td>
<td>12-18 months</td>
<td>Remission in all but one, also documented by PET/CT</td>
<td>2003</td>
<td>Calgolini et al., Yonsei Medical Journal 2003; 44:155-158 (59)</td>
<td></td>
</tr>
<tr>
<td>GCA/TA</td>
<td>Case series, prospective, open MTX vs. CYC add. to PRED, followed by MTX for maintenance</td>
<td>10 (4 TA, 6 GCA)</td>
<td>Resistant to high dose PRED, dose reduction impossible, pretreatment with AZA or MTX ineffective in 6), 2 newly diagnosed, severe manifestations no pretreatment</td>
<td>CYC(NH) 750 mg/m² i.v. every 3 weeks 6-12x, individually adapted (500-900 mg/m²), Maintenance in all with PRED / AZA, MTX/AZA (1) or MFMZA/AZA (1)</td>
<td>16–45 months</td>
<td>Remission in all but one, also documented by PET/CT</td>
<td>2004</td>
<td>Özen et al., J Peditr 2004; 150:72-76 (57)</td>
<td></td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>GCA Case report</td>
<td>1</td>
<td>with add. renal amyloidosis</td>
<td>Chlorambucil dosage not given</td>
<td>Not given</td>
<td>Response of GCA (AT) not given, focused on amyloidosis</td>
<td>2005</td>
<td>Cohen et al., Clin Nephrol 2001; 56:402-406 (58)</td>
<td></td>
</tr>
<tr>
<td>B) Biologic</td>
<td>B1) Anti-TNF Inflx embr</td>
<td>GCA Case series, 4</td>
<td>Severe disease, PRED resistant</td>
<td>3 infusions of IFX 3mg/kg bw week 0, 2, 6</td>
<td>5-6 months</td>
<td>3 complete response, 1 partial response, later relapse</td>
<td>2001</td>
<td>Canini et al., Arthr Rheum 2001; 44:2933-2935 (61)</td>
<td></td>
</tr>
<tr>
<td>GCA</td>
<td>Case series</td>
<td>2</td>
<td>Primary treatment in newly diagnosed GCA with IFX</td>
<td>NO PRED 7 patients ETA 2 x 25 mg sc/week changed later to IFX, 8 IFX 3-5 mg/kg bw i.v. week 0,2,4 ever 8 weeks</td>
<td>21,7 months median</td>
<td>1 complete and rapid response, 1 relapse under IFX, then start PRED</td>
<td>2003</td>
<td>Andoponoviov et al., Ann Rheum Dis 2003; 62:1116 (62)</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>Open-label multicentre prospective trial</td>
<td>15</td>
<td>Majority of patients resistant to MTX, MMF, AZA, CYC</td>
<td>NO PRED 2 x 25 mg sc/week changed later to IFX, 8 IFX 3-5 mg/kg bw i.v. week 0,2,4 ever 8 weeks</td>
<td>21,7 months median</td>
<td>25% sustained remission and PRED discontinued, 27% partial remissions, PRED reduced by at least 50%</td>
<td>2004</td>
<td>Hoffman et al., Arthr Rheum 2004; 50: 2296-2304 (63)</td>
<td></td>
</tr>
<tr>
<td>GCA</td>
<td>Case report</td>
<td>1</td>
<td>Monotherapy with IFX because of diabetes</td>
<td>5 mg/kg bw, intervals not given</td>
<td>6 months</td>
<td>Complete response</td>
<td>2005</td>
<td>Ulbrich et al., Clin Rheumatol 2006; 25:109-110 (64)</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>Case report</td>
<td>1</td>
<td>Resistant to high dose PRED and CYC pulses, oral CYC</td>
<td>5 mg/kg bw, intervals not given</td>
<td>6 months</td>
<td>Complete response</td>
<td>2005</td>
<td>Tato et al., International Angiology 2005; 24:304-307 (65)</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>Case report</td>
<td>2</td>
<td>Reduction of PRED not possible without relapse, in one case also resistance to MTX</td>
<td>3 mg/kg bw i.v. week 0, 2, 4, every 8 weeks. Later switch to ADA due to development of ANA (in remission)</td>
<td>Not given</td>
<td>Good clinical response, normalisation of ESR and CRP, ultrasound and MRA</td>
<td>2005</td>
<td>Dell Rossa et al., Rheumatology 2005; 44:1074-1075 (66)</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>Case report</td>
<td>1</td>
<td>Uveitis in TA resistant to PRED and MTX</td>
<td>3 mg/kg bw i.v. week 0, 2, 4, every 8 weeks with MTX 15 mg/week</td>
<td>12 months</td>
<td>Complete response, PRED tapered. MTX discontinued</td>
<td>2005</td>
<td>Meunski et al., Journal of Clin Rheumatol 2005; 11:213-215 (67)</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>Case report</td>
<td>1</td>
<td>Refractory to PRED and MTX</td>
<td>3 mg/kg bw i.v.</td>
<td>24 weeks</td>
<td>Complete response, PRED tapered. Remission achieved</td>
<td>2005</td>
<td>Tanaka et al., Intern Medicine DOI:10.2169/internamedicine.45.1377 (68)</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>Case report</td>
<td>4</td>
<td>Refractory to PRED, MTX, AZA, MMF, CYC, primary treatment in one</td>
<td>3 mg/kg bw i.v.</td>
<td>22 weeks to 3 years</td>
<td>PRED tapered, remission in all but one</td>
<td>2007</td>
<td>Karageorgaki et al., Clin Rheumatol 2007; 26:984-987 (69)</td>
<td></td>
</tr>
<tr>
<td>GCA (ION)</td>
<td>Case report</td>
<td>1</td>
<td>Ocular manifestation, PRED resistant</td>
<td>3 mg/kg bw i.v. 2 x, then switch to ETA for convenience (25 mg 2x/week s.c.)</td>
<td>Not given</td>
<td>Complete remission, visual acuity stable</td>
<td>2007</td>
<td>Torrente et al., Intern Med J 2007; 37:280-281 (70)</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Type of large-vessel vasculitis</td>
<td>Type of study</td>
<td>Number of patients</td>
<td>Previous treatments</td>
<td>Dosage</td>
<td>Observation period</td>
<td>Response</td>
<td>Year</td>
<td>Authors</td>
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<tr>
<td>GCA (AION)</td>
<td>Case report</td>
<td>1</td>
<td>Severe ocular manifestation, primary treatment</td>
<td>Newly diagnosed, no pre-treatment</td>
<td>5 mg/kg bw i.v., week 0/2 A then every 8 weeks</td>
<td>8 weeks</td>
<td>Improvement</td>
<td>2007</td>
<td>Benacchii et al., Recenti Progressi I Medicina 2007; 98:624-626 (84)</td>
</tr>
<tr>
<td>GCA</td>
<td>Multicentre international prospective PBO controlled-IFX for maintenance in GC induced remission</td>
<td>44</td>
<td></td>
<td></td>
<td>4-10 mg/kg bw i.v., ETA (n=9) 25 mg s.c. every week, 5 bolus, later switched to IFX</td>
<td>12 months</td>
<td>Remission and discontinuation of PRED in 60%, in 28% tapered below 10 mg, 50% could taper additionally given immunosuppressive agents</td>
<td>2008</td>
<td>Mollov et al., Ann Rheum Dis 2008; 67:1567-1569 (72)</td>
</tr>
<tr>
<td>TA</td>
<td>Retrospective case series</td>
<td>25</td>
<td>PRED reduction impossible</td>
<td></td>
<td>5 mg/kg bw i.v.</td>
<td>Not given</td>
<td>Remission</td>
<td>2007</td>
<td>Hoffman et al., Ann Intern Med 2007; 146:621-630 (71)</td>
</tr>
<tr>
<td>TA</td>
<td>Retrospective case series</td>
<td>4 children with TA</td>
<td>Resistant to PRED and immunosuppressives (MTX, AZA CYC)</td>
<td>MTX or AZA, two ADA (40 mg s.c. every 2 weeks)</td>
<td>Not given</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TA</td>
<td>Case report</td>
<td>1 child</td>
<td>With Crohn’s disease under AZA</td>
<td></td>
<td>5 mg/kg bw</td>
<td>Not given</td>
<td>Remission</td>
<td>2009</td>
<td>El-Matary et al., J Pediatrics 2009; 155:151 (74)</td>
</tr>
<tr>
<td>TA</td>
<td>Combined with Crohn’s</td>
<td>1</td>
<td>Resistant to PRED and AZA</td>
<td></td>
<td>5 mg/kg bw i.v.</td>
<td>Not given</td>
<td>Remission of both diseases, PRED reduced</td>
<td>2010</td>
<td>Calderon et al., Revista Espanola de enfermedades digestivas 2010; 102:144-148 (76)</td>
</tr>
<tr>
<td>TA</td>
<td>Associated with Crohn’s</td>
<td>1</td>
<td>Development of TA under IFX</td>
<td></td>
<td>5 mg/kg bw</td>
<td>Not given</td>
<td>Disease control in all</td>
<td>2010</td>
<td>Nunez et al., Bras J Rheumatol 2010; 50:291-298 (78)</td>
</tr>
<tr>
<td>TA</td>
<td>Case report</td>
<td>1</td>
<td>Unresponsive to conventional treatment (HCQ, tichodipine), PRED 1 mg/kg bw, MTX 15 mg/week orally</td>
<td></td>
<td>5 mg/kg bw week 0,2,4, then every 8 weeks</td>
<td>2 years</td>
<td>Remission, PRED and MTX reduced</td>
<td>2009</td>
<td>Maffei et al., Eur Rev Med Pharmacal Sci 2009; 13:63-65 (75)</td>
</tr>
<tr>
<td>TA</td>
<td>Case series, retrospective</td>
<td>2</td>
<td>PRED reduction impossible in spite of additional MTX</td>
<td></td>
<td>5 mg/kg bw i.v.</td>
<td>Not given</td>
<td>Remission, PRED reduction</td>
<td>2011</td>
<td>Buonomo et al., Rheumatol Int 2011; 31:93-95 (79)</td>
</tr>
<tr>
<td>TA</td>
<td>Case series, retrospective</td>
<td>2</td>
<td>Development of TA under IFX 3 mg/kg bw i.v. and MTX, one case later effectively treated with ADA</td>
<td></td>
<td>3 mg/kg bw</td>
<td>Not given</td>
<td></td>
<td>2011</td>
<td>Osman et al., Clin Rheumatol 2011; 30:703-706 (80)</td>
</tr>
<tr>
<td>TA</td>
<td>Case report</td>
<td>1</td>
<td>Patient with ulcerative colitis under budes steroids and sulfasalazine</td>
<td></td>
<td>5 mg/kg bw week 0,2,4, then every 8 weeks</td>
<td>12 months</td>
<td>Remission</td>
<td>2011</td>
<td>Gece et al., Inflamm Bowel Dis 2011; 17:E99-70 (81)</td>
</tr>
<tr>
<td>TA</td>
<td>Case series, retrospective</td>
<td>15</td>
<td>Active disease in spite of GC and additional immunosuppressive agents (7 MTX, 4 AZA)</td>
<td></td>
<td>5-5 mg/kg bw week 0,2,4, then every 8 weeks</td>
<td>12 months</td>
<td>Partial or good response in 87% at 3 months and 73% at 12 months. Clinical and biological activity decreased significantly, as did GC dose. AE: one tuberculosis, one severe infection, 2 infusion reactions</td>
<td>2011</td>
<td>Mekinian et al., Rheumatology in press (82)</td>
</tr>
<tr>
<td>TA</td>
<td>Case series, retrospective</td>
<td>5 plus literature review of 79</td>
<td>Resistant to PRED, AZA, MTX</td>
<td></td>
<td>5 mg/kg bw i.v.</td>
<td>3-32 months</td>
<td>Remission, PRED tapered in 3, one AE (cardiac failure)</td>
<td>2011</td>
<td>Comarmond et al., Autoimmunity Reviews 2011; IN PRESS (83)</td>
</tr>
<tr>
<td>Etanecoxib</td>
<td>Case report</td>
<td>1</td>
<td>Resistant to high dose GC</td>
<td></td>
<td>25 mg 2x/week s.c.</td>
<td>Not given</td>
<td>Patient stopped ETA thinking to be cured with concomitant relapse, after 6 months remission with 5 mg PRED further course not given</td>
<td>2003</td>
<td>Tan et al., Ann Rheum Dis 2003; 62:573-374 (85)</td>
</tr>
<tr>
<td>GCA</td>
<td>Case report</td>
<td>1</td>
<td>Occurrence of GCA under MTX and ETA for RA</td>
<td></td>
<td>25 mg 2x/week s.c.</td>
<td>Not given</td>
<td></td>
<td>2004</td>
<td>Seton J Rheumatol 2004; 31:1467 (86)</td>
</tr>
<tr>
<td>GCA</td>
<td>Prospective, double-blind PBO controlled study single centre</td>
<td>17</td>
<td>GC side effects</td>
<td></td>
<td>25 mg 2x/week s.c.</td>
<td>12 months</td>
<td>50% in ETA group without PRED, 22,2% in PBO group (significant) and in remission</td>
<td>2008</td>
<td>Martinez-Taboada et al., Ann Rheum Dis 2008; 67:625-630 (87)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>GCA case report</td>
<td>1</td>
<td>Resist to 60 mg PRED (ocular manifestation)</td>
<td></td>
<td>Not given</td>
<td>6 months</td>
<td>Complete remission, PRED reduced to 12.5 mg/day</td>
<td>2007</td>
<td>Ahmed et al., Clin Rheumatol 2007; 26:1353-1355 (88)</td>
</tr>
<tr>
<td>GCA</td>
<td>Case report</td>
<td>1</td>
<td>Patient with AT resistant to PRED MTX and ETA switched to ADA for RA</td>
<td></td>
<td>Not given</td>
<td>6 months</td>
<td>Development of GCA under ADA/PRED</td>
<td>2007</td>
<td>Leydet-Quilici et al., Joint Bone Spine 2007; 74:299-305 (89)</td>
</tr>
<tr>
<td>Medication</td>
<td>Type of study</td>
<td>Number of patients</td>
<td>Previous treatments</td>
<td>Dosage</td>
<td>Observation period</td>
<td>Response</td>
<td>Year</td>
<td>Authors</td>
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</table>
| **B.2.) Anti-IL-6**  
Toxicilumab | TA | Case report | 1 | Resistant to high dose PRED and iv. MP | 4 mg/kg bw every 4 weeks i.v., later increased to 8 mg | Not given | 2008 | Nishimoto et al., Arthritis Rheumatology 2008; 58:1197-1200 (90) |
| | GCA/TA | Case series, retrospective | 7 (2 TA, 5 GCA) | Resistant to PRED and MTX (2), PRED alone (2), PRED, AZA, MTX, IFX (1), Primary treatment in 2 | 8 mg/kg bw every 4 weeks i.v. | 3 months (MRA) | 2011 | Seitz et al., Swiss Medical Weekly 2011; 141; w13156 (91) |
| | GCA | Case series, retrospective | 3 | Rescue treatment after PRED resistance and contraindications to MTX, AZA and other immunosuppressive agents | 8 mg/kg bw every 4 weeks i.v. | Not given | 2011 | Beyer et al., Ann Rheum Dis 2011; 70:1874-1875 (92) |
| | GCA | Case series | 2 | PRED and MTX resistant/dependant (PRED could not be reduced below 25 mg without relapse) | 8 mg/g bw every 4 weeks i.v. | 7 months | 2011 | Sciocia et al., J Rheumatol 2011; 38:2100-2101 (93) |
| | GCA/TA | Case series, retrospective | 4 (2 TA, 2 GCA) | Resistant to high dose PRED and MTX | 8 mg/kg bw every 4 weeks | 7-11 months | 2012 | Salvarani et al., Rheumatology 2012; 51:151-156 (94) |
| **B.3.) Anti-B-Cell**  
Rituximab | GCA | Case report | 1 | Resistant to PRED, AZA not tolerated | 1000 mg once i.v. | 1 month | 2005 | Bhatia et al., Ann Rheum Dis 2005; 64:1099-1100 (95) |
| | GCA | Case report | 1 | GC could not be tapered due to additional neutropenia | 1000 mg day 1 and 15 mg every 15 days | 1 month (too short as the authors state themselves) | 2007 | Mayrbaierl et al., Clin Rheumatol 2007; 26:1597-1598 (96) |
| | TA | Case report | 3 | Article on B cell homeostasis in TA, 3 of 17 patients treated with RTX. These were resistant to | 1000 mg day 1 and 15 mg every 15 days | Online supplement Ansehen | All in remission, also proven by PET/CT | 2012 | Hoyer et al., Ann Rheum Dis 2012; 71:75-79 and online supplement (97) |
| **C.) Other**  
Autologous stem cell transplantation | TA | Case report | 1 | Resistant to PRED, MMF, then stem cell mobilisation and ASCT | CYC/G-CSF, CYC/ATG | 400 days | 2004 | Volland et al., Rheumatology 2004; 43:1308-1309 (99) |
| | TA | Case report | 1 | Resistant to PRED, AZA, YC, MEF, ETA, CSA, IFX, ANAKISRA (various combinations) | CYC/ATG | 12 months | 2005 | Köntger et al., Clin Rheumatol 2005; 24:485-489 (100) |
| | TA | Registry data | 1 (of 15 with vasculitis) | Same patient as above | Same patient as above | 16 months | 2007 | Dukeler et al., Ann Rheum Dis 2009; 70:237-241 (101) |
| **D.) MIXED**  
Retrospective case series | TA | Single centre series | 108 | 77 patients received GC, 33 in combination with immunosuppressive drugs such as MTX or AZA | Not specified | Not given | 2005 | Park et al., Scand J Rheumatol 2005; 34:284-292 (104) |
| | TA | Retrospective case series | 248 | Only 9% treated with GC alone, 84% needed additional immunosuppressives | 63% MTX, 22% AZA, 13% CYC, 6% LIF, 4% MMF, 2% anti-TNF | Not given | Not specified | 2009 | Bicakcioglu et al., Clin Exp Rheumatol 2009; 27 (Suppl. 52) S59-S6 (103) |
| | TA | Retrospective case series (France) | 82 | 46% required 1 ore more additional immunosuppressive agents (28% AZA, 25.6% MTX, 7.3% MMF, 5.4% monthly CYC pulses, Anti-TNF in a single patient (IFX)) | Not given | Not given | 2010 | Armaud et al., Medicine 2010; 89:1-17 (102) |

of candida sepsis after being switched to ETA. Katoh et al. describe a patient with Crohn’s disease who developed TA under MTX due to ETA. Katoh et al. also describe a patient with rheumatoid arthritis who developed GCA under ADA and prednisolone (PRED) (89). Seton describes a patient developing TA under MTX and ETA for rheumatoid arthritis (86). Rimar et al. describe two patients who were under treatment for RA with MTX developed GCA (29).

One recent retrospective case series from France described 82 TA patients, 53% (white Caucasian) and 44% (black African) of whom after primary GC treatment required additional immunosuppressive agents. Twenty-eight percent received AZA, 25.6% MTX, 7.3% MMF, 5.4% monthly CYC pulses. Infliximab was administered to one single patient. As treatment was not in the focus of that study (which examined racial differences in disease activity and outcome), differences in the efficacy of the immunosuppressives are not reported (102). Similarly, in a previous retrospective multicentre analysis of patients with TA in Turkey with 248 individuals, 84% required additional immunosuppressive agents to their primary GC regimen. Most frequently MTX was used (84%), followed by AZA (22%), and CYC (13%). LEF was used in 6% and MMF in 3%. Three resistant cases were treated with TNF inhibitors (103). Another retrospective series with 108 patients from Korea also reported high rate of GC dependent or even resistant cases in TA, with a 48% rate of patients receiving steroid sparing immunosuppressives such as MTX or AZA, which are not specified further (104). In a retrospective single centre analysis from Brazil, of 30 patients only 10 achieved disease control with GC alone. 12 patients received MTX (median 8.8 mg/week) additionally and 58% had a good response, 2 patients resistant to this combination received CYC 2 mg/kg bw/day orally without response (105). There were prospective open or randomised trials, 6 with MTX, 1 with azathioprine, 3 with IFX and 1 with ETA.

**Prospective open and randomised trials**

**Methotrexate (MTX)**

Our literature search revealed two prospective open (18, 20), two single centre prospective controlled double blind trials (21, 26) and two prospective randomised trials with two centres or designed as multicentre trials (25, 27).

The two prospective open trials included 11 and 43 patients, respectively, however, among the 43 patients in the study by Feinberg et al., only 3 had GCA, the others were suffering from PMR. Whereas the study by Hernandez-Garcia included newly diagnosed and previously untreated patients, Feinberg et al. included patients who were adequately controlled with prednisolone. The patients in the Hernandez-Garcia study received 10 mg MTX/week orally, those in the Feinberg study 7.5 mg. Garcia-Hernandez et al. concluded that MTX is safe and steroid-sparing, as 10 of the 11 patients finally were able to discontinue their GC. The observation period was 22–37 months. In the Feinberg et al. trial, with a shorter observation period of 9 months and a lower MTX dosage as well as a difficult-to-treat GC resistant patient population, no steroid-sparing effect for the whole group could be shown. However, as the patient number with GCA was very small, a positive effect of MTX in this subgroup could not be excluded. In the two prospective randomised single centre trials, 40 and 21 patients were included. Also in one of these trials, namely the one published by Van der Veen et al., only 6 of the 40 patients had GCA in overlap with PMR, the other 34 patients had PMR only (21). They included patients with active, newly diagnosed and previously untreated disease, the patients in the MTX arm were treated with 7.5 mg MTX/week orally. The observation period was 21 weeks. Spiera et al. included 21 GCA patients with active, newly diagnosed and previously untreated disease, the patients in the MTX arm also received 7.5 mg MTX/week orally, but in case of flare this was increased up to a maximum of 20 mg, if necessary. The observation period was 12 months (26). Both studies came to the conclusion that although prednisolone could be reduced by more than 50% of the baseline dosage, MTX has no steroid-sparing effect, as there were no differences between the two arms. Adverse events were not different, either.

Finally, the two prospective two-centre (27) or multicentre (25) trials included 42 and 98 patients respectively. Both included GCA patients who were newly diagnosed, active and untreated. The dosage of MTX in the active treatment arm was 10 and 15 mg/week orally. Both treatment arms received prednisolone, either 60 mg or 1 mg/kg bw. The observation period was 12 months in the study by Jover et al. and 24 months in the Hoffman et al. trial. The study by Jover et al. showed that the number of relapses was significantly reduced in the MTX arm and that the cumulative GC doses were also significantly lower in the MTX treated group. There was no difference in the number of adverse events between the two groups. In contrast, the study by Hoffman et al. came to the conclusion that except for a reduction of relapses in the form of polymyalgia rheumatica, MTX did not reduce the cumulative GC dosage, nor did it reduce the number of relapses, the probability of achieving remission or morbidity. Again, there was no difference in adverse events between the groups.

**Meta-analysis of the randomised MTX trials**

In 2007, Mahr et al. published a meta-analysis of the MTX trials published so far (106). They aimed at a re-evaluation of the efficacy and safety of low-dose MTX in GCA. For this purpose, they performed an individual patient data meta-analysis of three of the above mentioned randomised placebo-controlled trials (25-27) with 84 patients in the MTX arms and 77 in the placebo arms of the studies over a median observation period of 54.7 weeks. The trial by van der Veen et al. was excluded as the original data were no longer available (21). Use of MTX resulted in a significant reduction in the cumulative GC dose by 842
mg within 48 weeks. Moreover, MTX treatment was associated with a significantly higher probability of achieving sustained discontinuation of GC for more than 24 weeks. Three point six individuals and 4.7 individuals needed to be treated with MTX in order to prevent the occurrence of one first or one second relapse, respectively. MTX reduces the risk of a first relapse by 35% and the risk of a second relapse by 51%. A subgroup analysis according to age, gender, positivity of temporal artery biopsy, relapse type (cranial or non-cranial) and weeks from MTX initiation for relapse did not reveal any differences. The analysis of duration of follow-up at different time points revealed that the superiority of the treatment effect of MTX over placebo appears only after 24 to 36 weeks. The authors conclude that MTX is effective as glucocorticoid-sparing agent and lowers the risk of relapse. It should be considered as a therapeutic option in addition to standard-of-care treatment with GC for patients with GCA.

Azathioprine (AZA)
For azathioprine, only one prospective, double-blind PBO controlled single centre trial was published. It included 31 patients with GCA or PMR/GCA overlap, whose disease activity was controlled with 5 mg prednisolone for at least 3 months. The aim of the study was to show if AZA had a steroid-sparing effect in PMR/GCA overlap during the maintenance phase (35). Sixteen patients were in the AZA arm and 17 in the placebo arm. The patients on AZA received 150 mg daily orally, in combination with prednisolone according to a “standard regimen” which was not specified. However, the patients were stratified according to their prednisolone doses. The observation period was 52 weeks. There was a significant reduction in the prednisolone dose at week 52, in favour of the AZA group.

Cyclosporine A (CSA)
There is one randomised controlled trial with CSA, which included 60 patients with newly diagnosed and untreated GCA. For an observation period of 12 months, the patients all received prednisolone according to a prede-
was started with 40 to 60 mg/day and then reduced according to an algorithm which was provided in the publication. The observation period was 54 weeks, and 22 centres in the USA and Europe participated in the study. The randomisation was 2:1 for IFX. Sixteen patients were assigned to PRED plus placebo, 28 to PRED plus IFX. As a result, IFX did not decrease the number of relapses at week 22, nor did it decrease the cumulative PRED dosage. There were slightly more infections with IFX, but this difference was not significant. In conclusion, the authors state that the sample is too small to rule out modest effects of IFX and included only newly diagnosed patients, however, a role for IFX as a therapeutic agent for maintenance treatment in GCA is unlikely.

*Etanercept (ETA)*

ETA is a fusion protein of two p75 subunits of the TNF receptor linked to the Fc portion of human IgG1. It was approved for rheumatoid arthritis in 1999. The first case report on ETA for GCA/TA appeared in 2003, however, in the following publications, ETA was given in case series and open prospective studies before or after IFX or in studies where also IFX was analysed (63, 70, 72). In most of these, it proved effective.

There is one randomised prospective double-blind placebo-controlled single centre trial with 17 GCA patients who needed alternative treatments due to GC side effects. They received 25 mg ETA 2x/week s.c. Observation period was 12 months. Eight patients received ETA, 9 PBO. The initial prednisolone dosage varied. After 12 months, 50% of the patients in the ETA group and 22% in the PBO group were able to control the disease without GC therapy (not significant). Patients in the ETA group had a significantly lower dose of accumulated prednisolone during the first year of treatment. There were no differences in number and type of adverse events. The limited number of patients does not allow to draw definitive conclusions, as the authors state.

**Summary of data for steroid-resistant or steroid-dependent GCA/TA**

Of the 64 publications on steroid sparing immunosuppressives for GCA/TA found in the literature, 50 (79%) reported on patients who were either resistant to or dependent on GC (17, 20, 24, 28, 33, 38, 40, 41, 44, 46-49, 51-53, 55, 56, 58-63, 65-70, 72, 73, 75, 78-80, 82, 83, 85, 86, 88-97, 99, 100). Among these, there is one prospective trial. It is an open-label trial for TA refractory to immunosuppressives such as MTX, MMF, AZA, CYC, or PRED (5 of 15 patients), who were treated with either ETA or IFX (63).

Of the MTX treated patients reported in the literature, 111 had GCA (98%). Of these, only 6 (5%) were refractory to GC or immunosuppressive agents. Only 2 TA patients were treated with MTX (1.8%), and both were refractory to GC. Fifty-one GCA patients were treated with AZA (100%), only 3 (5.9%) were treatment-resistant. There are no publications on TA patients with AZA. The trial on antimalarials (HCQ) included 36 GCA patients, all (100%) were refractory to standard GC. There are no reports on TA with antimalarials. Forty-four of the patients with CSA (93.6%) had GCA, only 14 (32%) were treatment resistant. Three TA patients also received CSA (6.8%), all were GC resistant. Two TA and no GCA patients with Lef were published, both were resistant to PRED and MTX or CYC. Exclusively TA patients received MMF (100%), 21 of 32 were resistant to GC (65.6%), 50% also to other immunosuppressives. Nineteen of the patients with CYC had GCA (70.4%), 8 TA (29.6%). All GCA patients (100%) and 2 of the 8 TA patients were treatment resistant (25%), 2 TA and 4 GCA patients were even resistant to MTX or AZA before. As for IFX, 33 patients had GCA (26.8%) and 90 TA (73.2%). Of the GCA patients, only 5 were treatment-resistant (15.2%), mostly to PRED only. Of the TA patients, 82 were treatment resistant (91%), almost all to PRED plus other immunosuppressive agents. For ETA, only GCA patients are reported (n=10, 100%), only one was resistant to higher doses of GC (10%). With TCZ, 12 GCA (70.6%) and 5 TA patients (29.4%) were reported, all but 2 GCA patients (1.7%) had not responded to PRED or PRED plus immunosuppressive agents before. Two GC (40%) and 3 TA (60%) patients have been treated with RTX so far, the GCA patients were all refractory to GC (100%), whereas the TA patients all had received other immunosuppressive agents additionally before. The same also holds true for the 2 TA patients who underwent autologous stem cell transplantation. The percentages of the patients with TA and GCA

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*Fig. 1. Distribution of patients on medications. Columns show total number of patients for GCA and TA as well as the number of patients regarded as resistant to GC treatment, respectively.*

<p>| MTX | AZA | HCQ | CSA | LEF | MMF | CYC | IFX | ETA | TCZ | RTX | ASCT | S-123 |
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for each medication and the percentages of those in each group being GC-resistant are depicted in Figure 1. There are four larger retrospective case series on the subject of steroid dependency or resistance, one with antimalarials for GCA (36 patients) (60), two on MMF for TA (10 and 21 patients) (49, 50), one on CYC for GCA and TA (10 patients, 4 TA, 6 GCA) (58), one on IFX and ETA for TA (25 patients) (72). For the antimalarials, a “recovery rate” of 58% is described, for MMF significant decreases in disease activity (in the second series measured by the Indian Takayasu Arteritis Activity Score ITAS) and PRED dosage, in the CYC series a remission in all but one patient (90%) also documented by PET/CT, and in the IFX/ITA series a 60% remission rate and 28% significantly decreased PRED dosage is described. It is impossible to distinguish exactly between GC-resistant and GC-dependent cases, as no clear definitions for resistance or dependency were provided at all or they were very heterogeneous or both were taken together in one series or trial and not regarded separately. Furthermore, the definitions of complete and partial remissions also vary considerably, if specified at all.

**Discussion**

The mainstay in the management of GCA/TA are high dose GC for induction of remission, and low dose steroids (5 mg PRED /day or lower) for maintenance of remission for 1–2 years, as stated in the recent EULAR recommendations (5). However, in some patients, a reduction of GC under 5 mg/day prednisolone equivalent may be impossible (GC dependency) without relapse or even remission not achievable (GC resistance). This percentage of patients is estimated for GCA to be 40.8% to 48% (7, 107). In these patients, additional remission-inducing agents are needed. Furthermore, additional steroid-sparing agents for maintenance of remission may be necessary in this difficult-to-treat patient population, in order to get the GC dose below the “Cushing threshold” and avoid adverse events such as infections, osteoporosis, diabetes, or cataract. Similarly, 46 to 84% of the TA patients in retrospective case series from Korea, Turkey and France were described to require additional immunosuppressive treatment in order to achieve remission and taper GC (102-104).

Although GCA is the most frequent form of systemic vasculitis, with an annual incidence of 27/100.000 in Scandinavia and 7–11/100.000 in Mediterranean countries (108), as opposed to TA, with an annual incidence of 0.7 and a prevalence of 5–7 per million inhabitants in a recent British study (109), there are only few prospective open or randomised trials on steroid sparing agents for the treatment of GCA or TA resistant to conventional high-dose steroids or requiring prolonged GC doses above the Cushing threshold.

Some trials analysed PMR and GCA simultaneously, which may have hampered the results (20, 21). MTX is an evidence-based and generally recommended steroid sparing and even remission-inducing agent in granulomatosis with polyangiitis (Wegener) (GPA) (110, 111). In the MTX trials for GCA/TA, different patient populations were included (newly diagnosed untreated [18, 25-27], GC resistant [20]). Furthermore, the dosages of MTX were quite low. Most trials and case reports/case series used MTX dosages between 7.5 and 12 mg/week orally. In rheumatoid arthritis, or for the remission inducing treatment of localised forms of GPA (Wegener) (112), higher doses are used (15 mg to 30 mg/week).

Another matter of concern is the mode of application of MTX, since probably a parenteral application is more effective compared to oral intake (113) due to better bioavailability (114). The patient numbers in all trials are relatively small. The largest study included 98 patients (25). Observation periods and follow-up, ranging from 3 to 37 months with a median of 11 months may often have been too short to detect differences. There is an intensive debate on the significance and necessity of MTX as a steroid sparing agent in GCA. This is expressed in several critical comments and discussions in the literature over the last 15 years (29, 115, 116).

In our opinion, the meta-analysis by Mahr et al. (106) clearly shows that MTX should be the first-line agent if a steroid-sparing medication is regarded necessary such as in case of contraindications for GC or impossibility of GC reduction. To clarify if MTX should already be given in combination with the high dose GC for induction of remission to facilitate GC reduction and prevent relapses, further, well-designed and large trials will be necessary. In a recent review in this journal, Spies et al. have summarised the available literature on MTX for large-vessel vasculitides and polymyalgia rheumatica and came to the conclusion that 10–15 mg of oral MTX have a modest and delayed effect in reducing relapse rate and lowering the cumulative GC dose. MTX may be used as adjunctive therapy in GC resistance or complications. They suggest that further attempts should be made for a better identification of patients with GC-refractory courses and a more precise formulation of guidelines on indication, optimal dosing and duration (116).

Azathioprine also is widely used as steroid sparing agent not only in connective tissue diseases such as SLE (117, 118), but also in some forms of vasculitis, where the evidence for its efficacy is quite good, such as for example Behçet’s disease (119, 120). However, in GCA/TA only one older randomised study is available (35). This revealed a superiority of the AZA arm compared to prednisolone alone in patients with GCA or PMR or both with stable remission of disease under 5 mg prednisolone equivalent or more. Until now, however, no larger multicentre trials followed, possibly because of a risk of elevated liver enzymes. One prospective trial was prematurely stopped because of this adverse event (36).

The use of CSA was discouraged by a randomised study in 2006, which did not show any advantage over placebo but an increase in adverse events (increasing creatinine and hypertension) (44). Leflunomide was not used in a considerable number of patients to date, the same also holds true for chlorambucil. The latter may have too many adverse effects such as cytopenias and secondary malignancy for a
more widespread use. Antimalarials were analysed in a retrospective French study (60), however, there was no placebo control and all patients received GC in parallel. Hence, it is impossible to judge if the recovery rate of 58% has to be ascribed to the antimalarials or not. To date, antimalarials are not recommended for the use in other systemic vasculitides which may be the reason why they were not used by others as a steroid-sparing agent in GCA/TA. Furthermore, the publication appeared in French language, which probably hindered its circulation. For mycophenolate mofetil (MMF), 3 case series exist, all on TA and almost exclusively steroid dependent patients were treated, one case series also included patients with MMF as initial treatment. In the steroid dependent cases, GC could be decreased, in the case series including also patients with primary MMF treatment GC were also reduced, but is it impossible to differentiate between the effects of GC alone and MMF. Disease activity also decreased in all patients (48-50).

Cyclophosphamide, astonishingly, is not well investigated in GCA/TA, although it is the major remission-inducing agent in severe manifestations of other systemic vasculitides such as GPA (Wegener) (121). Especially in CNS manifestations of Behçet’s disease, cyclophosphamide is also recommended (122). There are no prospective controlled trials for GCA/TA, and the largest case series published to date comprises 10 patients, 4 with TA and 6 with GCA (58). Here, 8 patients had refractory disease, 2 severe organ threatening manifestations. All but one achieved remission and prednisolone could be reduced, however, all patients obtained a steroid-sparing maintenance treatment (mostly AZA, some MTX, one MMF). In this case series, remission also was documented by PET/CT. Cyclophosphamide as intravenous pulses according to the NIH (123) or the Eurolupus protocol (124, 125) is relatively safe and effective. In younger patients, fertility may be a matter of concern, as well as secondary malignancies, which tend to occur with an increased frequency at cumulative CYC doses above 30 g (126). Infections, especially in combination with GC, may also be a problem and supportive antibiotic treatment is recommended (cotrimoxazole as prophylaxis against pneumocystis jiroveci pneumonia), as are prophylactic vaccinations (pneumococci, haemophilus, influenza). Here, too a randomised trial for CYC against placebo for induction of remission in patients with severe manifestations of GCA or TA (CNS, ocular, gastrointestinal vessels) would be desirable, especially in the light of cost-effectiveness when compared to biologics.

Concerning biological agents, most reports are on anti-TNF agents, among these, mostly on IFX which was the first one available in 1998. There is one prospective randomised trial with IFX versus GC alone for maintenance treatment of newly diagnosed GCA in GC induced remission (71). Another prospective open-label multicentre trial on treatment-resistant TA uses ETA and IFX and later switched some of the ETA patients to IFX. Whereas the randomised study did not find any difference between IFX or placebo and was stopped prematurely, the open trial showed a marked reduction in GC dose and remission rate (partial and complete) of approx. 50% (63). The main difference between the trials (besides the focus on two different entities, namely GCA and TA and the open non randomised trial merges ETA and IFX) is that the randomised trial used IFX as maintenance treatment in patients in remission, whereas the TA patients in the second trial were resistant to PRED or, half of them, also to diverse steroid-sparing immunosuppressives. However, the results of the open-label trial are difficult to interpret as IFX and ETA were not used systematically but merged. ETA may be less effective than IFX, as ETA is a fusion protein of the soluble TNF receptor and IFX a monoclonal antibody against TNF alpha. ETA has been shown to be less effective for uveitis and inflammatory bowel disease than monoclonal anti-TNF alpha antibodies (127-129). The second prospective, randomised placebo-controlled trial uses ETA for GCA patients who due to side effects could not be treated with adequate doses of GC. The ETA group had significantly lower GC doses than the PBO group at the end of the study, and relapse rate also was lower (not significant). The authors conclude that their sample size (17 patients) probably was too small to detect further differences (87). In his editorial comment on the study by Hoffman et al. of 2007, Luqmani (130) points out that the confidence intervals were very wide and hence the sample size also in the prospective randomised trial with IFX may have been far too small to detect treatment effects. He proposes a trial for GCA with three treatment groups: standard-dose prolonged GC, short dose GC in combination with IFX and a third arm with placebo only after successful induction of remission with GC. Most recently, Comarmond et al. have published a review of the literature on anti-TNF-alpha agents in refractory TA (83). All patients of 79 with TA except one published in case reports and case series thus far had been inadequately controlled by GC and other immunosuppressive agents before receiving anti-TNF-alpha agents. They would thus probably be classified as “steroid-resistant”. The most commonly used anti-TNF agent was IFX in a dosage of 5 mg/kg bw, in combination with either MTX or AZA. Thirty-seven per cent of the patients achieved complete remission, while 53.5% partial remission. GC could be tapered in 52% and discontinued in 40%. Adverse events were observed in 20%, mostly infections, followed by hypersensitivity reactions. One may hypothesise that anti-TNF agents may be useful in the setting of induction of remission in GC-resistant cases of GCA or TA only, a question which has not been addressed in the prospective trials until now. From an immunological point of view, their use in GCA and TA appears reasonable, as TNF alpha was found in abundance in affected temporal arteries (131).

IL-6 antagonists have been used recently in several case reports and case series. This is reasonable from a pathogenetical point of view, as IL-6 appears to be one of the key players in the pathogenesis of GCA and TA. It is present in the wall of the inflamed vessels (132).
Tocilizumab was mostly applied to patients with treatment-resistant GCA or TA, and to date no inefficacy was reported. Rituximab has been exclusively used in a very limited number of treatment-resistant cases of GCA (n=2) or TA (n=3). Until recently, the role of B-cells in TA and GCA was unclear, and their role in the pathogenesis of large-vessel vasculitides appeared to be limited, as macrophages, dendritic cells and CD4+CD28- T-cells dominate the inflammatory infiltrate and produce IFN gamma, IL-1β, IL-6, TNF alpha and metalloproteinases and induce the production of PDGF. In 2011, Hoyer et al. showed that the number and frequency of antibody secreting CD19+/CD20-/CD27(high) plasmablasts is increased in the peripheral blood of patients with clinically active TA, as well as general B-cell hyperactivity and that these patients can be treated successfully with rituximab (97). Although this at first seems illogical as the plasmablasts are CD20 negative and rituximab binds to CD20, plasmablasts differentiate from CD20+ B-cells, so rituximab depletes their B-cell pool.

As “ultima ratio” autologous stem cell transplantation was performed in 2 patients reported in the literature so far. One had received even cyclophosphamide and anti-TNF agents and almost all available immunosuppressives without clinical effect (100), the other had been refractory to Pred, MTX, MMF (99). Both patients achieved remission after ASCT and were able to reduce their baseline immunosuppressive treatments. GCA patients should not undergo ASCT as they are normally older than 60 years and have comorbidities which unacceptably increase transplantation associated morbidity and mortality. As transplantation associated mortality in autoimmune diseases lies between 3 and 7%, this approach in our opinion should be reserved for otherwise healthy patients with TA who do not respond even to biological agents. In this issue of *Clin Exp Rheumatol*, Italian recommendations for the treatment of large-vessel vasculitides with biological agents are published (see p. S139). These recommendations show how difficult it is to make definite statements, when clear-cut evidence is missing. The EULAR recommendations for GCA and TA were published in 2009 (5), and until 2011 not much more evidence adding to that underlying the EULAR recommendations appeared. The Italian recommendations focus on biological agents and omit recommendations for alternative steroid-sparing or remission-inducing agents. The only additional major difference between the Italian and the EULAR recommendations is that in the Italian Behçet’s disease, Cogan syndrome and isolated CNS angiitis have been included under the headline “large-vessel vasculitis”. Normally, the term large-vessel vasculitis is reserved for GCA and TA, two vasculitides which almost exclusively affect the aorta and its major branches. CNS angiitis is mostly affecting small arteries, and Behçet’s disease affects vessels of all sizes, also veins, but small vessels are much more commonly affected than large ones. Cogan syndrome is a very special entity consisting of interstitial keratitis or panuveitis associated with inner ear deafness.

For GCA biological agents (namely TNF inhibitors) are not recommended as first line treatment or monotherapy because of lack of evidence. They may be used in patients with more than 2 flares or relapses despite adequate treatment with GC and one or more additional immunosuppressive agents (MTX 15–20 mg/week, AZA 2–2.5 mg/day). Similarly, for TA due to lack of evidence, no monotherapy with biological agents (TNF inhibitors) is encouraged, nor is the use as first line treatment. They may be used in patients with persisting disease activity for more than 6 months or more than 2 flares or relapse despite GC and one or more immunosuppressive agent (MTX 20 mg/week, AZA 2–2.5 mg/day, MMF 2 g/day for 4–6 months).

For both diseases, the efficacy of biological agents is to be assessed after 4 months and in case of lack of improvement it should be discontinued. Everybody would agree that there is no evidence for monotherapy with biological agents, and that the evidence for their efficacy as a primary steroid-sparing treatment is sparse. However, with the exception of methotrexate, the evidence for the use of immunosuppressive agents as remission-inducing or steroid-sparing agents is lacking, too. Hence, the recommendations for the immunosuppressive agents, which must have been ineffective before initiating treatment with biological agents, are more eminence- than evidence-based, as are the recommendations for the MTX dosages, because the trials and case series used lower doses of MTX than those recommended by the Italian specialists. One may ask why cyclophosphamide was not considered in the recommendations and why it was not considered as a primary “third-line” agent in steroid resistant or dependent GCA or TA after inefficacy of GC and one less aggressive immunosuppressive agent. To date, it is impossible to decide if CYC has more, comparable or even less adverse effects than anti-TNF alpha biologicals. We suppose that with the EUROLUPUS protocol and adequate antibiotic prophylaxis, this will not be the case, and regarding the existing case series and experiences in other systemic vasculitides it may be as effective but much cheaper than the biologicals. However, this remains to be proven by appropriately designed prospective trials.

In summary, steroid-resistant GCA and TA clearly exist, and prospective randomised placebo-controlled trials for their treatment are urgently needed. Unfortunately, the trials which have been published to date have included very heterogeneous patient groups. The numbers of patients are too small to draw definite conclusions in almost all of them, and in the MTX trials, the dosage of the active medication probably was too low. Furthermore, we suggest to include GC-resistant patients into trials with agents for remission-induction, whereas trials testing GC-sparing properties, should include newly diagnosed patients. Of course, in the case of trials for induction of remission, a uniform and clear-cut definition of GC-resistance is mandatory – as was suggested for GC-dependence by Camelino et al. (28) or van der Veen et al. (21) who defined GC-dependence and GC-resistance as an impossibility of
reducing prednisolone under 7.5 mg/day or under 20 mg/day, respectively, without increase in disease activity. Moreover, a kind of disease activity score would be desirable, such as for example the Indian Takayasu Arteritis Activity Score (ITAS) used by Goel et al. (50). Recently, a Takayasu Disease Extent Score was published (133), which may also be useful for future trials. To our knowledge, for GCA, no such validated clinical activity index was developed so far.

We should focus on developing a strong network of clinicians and researchers interested in GCA/TA and design appropriate prospective randomised trials which hopefully answer the most urgent questions in the future. In this respect, we should follow the example of EUVAS (the European vasculitis study group, http://www.vasculitis.org/), designing, completing and publishing studies on the treatment of ANCA associated vasculitides – this is probably the way to optimise the treatment of patients with large- vessel vasculitides, too.

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