The management of large vessel vasculitides

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Abstract

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) represent the most common large vessel vasculitides (LVV). An early recognition of these conditions is crucial in order to start a prompt treatment to prevent severe ischemic complications, such as irreversible visual loss in GCA and cardiovascular or cerebrovascular accidents in TAK. Isolated glucocorticoids (GCs) still remain the cornerstone of GCA therapy. However, long-term treatment with GCs is burdened by an important toxicity. Furthermore, relapses are frequent during the follow-up period and relapsing patients have to cope with a longer duration of the GC therapy and a higher cumulative GC dose. On the other hand, TAK treatment usually relies on immunosuppressors in addition to GCs from the beginning. Also, since TAK patients are in general young women with a progressive disease, it is essential to treat this vasculitis with steroid-sparing drugs in order to avoid excessive GC exposure.

For this reason, efforts have been made to discover new therapeutic options able to reduce the cumulative GC dose that is strictly related to GC-toxicity. In recent years, new advances in the management of LVV have become available and have changed the therapeutic approach to these diseases. The aim of this review is to report new evidence of treatment efficacy and safety in LVV.

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Introduction

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) represent the most common large vessel vasculitides (LVV), a group of diseases which primarily affect the aorta and its major branches.[1] They both are characterized by inflammation of large and medium-sized vessels, which could lead over time to structural damage and changes in their diameter (stenosis and/or dilatation). The spectrum of clinical manifestations is broad, ranging from non-specific constitutional symptoms to more characteristic manifestations. Early detection of these conditions is crucial in order to start a prompt treatment to prevent severe ischemic complications, such as irreversible visual loss in GCA. GCA typically affects elderly people,[2] while TAK is much more common in women below the age of 40.

Over the last few years, new advances in the management of LVV have become available and have changed the therapeutic approach to these diseases. Isolated glucocorticoids (GCs) still remain the cornerstone of GCA therapy, while the use of steroid-sparing drugs is limited to steroid-resistant cases. On the other hand, TAK treatment usually relies on immunosuppressors in addition to GCs from the beginning.[3]

The aim of this review is to report new evidence of treatment efficacy and safety in LVV.

Management of giant cell arteritis

Role of glucocorticoids

In most cases, adequate GC doses quickly suppress clinical features and prevent the risk of ischemic complications, such as visual loss or cerebrovascular accidents, which occur in a minority of patients once the GC therapy has been started.[2,4,5] However, long-term treatment with GCs is burdened by an important toxicity, since side effects are observed in more than 50% of patients.[6] Furthermore, relapses are frequent during the follow-up period (ranging from 34% to 74.5%)[7] and relapsing patients have to cope with a longer duration of the GC therapy and a higher cumulative GC dose. The most important adverse events are infections, diabetes, bone fractures (vertebral fractures, above all) and cataracts.[6] For this reason, efforts have been made to discover new therapeutic options able to reduce the cumulative GC dose that is strictly related to GC-toxicity.

Role of non-biological immunosuppressive drugs

The role of *methotrexate* (MTX) as a steroid-sparing agent in GCA has been assessed in 3 randomized controlled trials (RCTs)

and 1 meta-analysis, with conflicting results. In the first RCT Jover *et al.* showed that MTX in addition to GCs was able to reduce the number of relapses and the total cumulative GC dose in GCA patients.[8] Conversely, the other two studies were negative, not supporting the additional use of MTX to control disease activity or to decrease the cumulative dose and toxicity of GCs.[9,10] In the meta-analysis of the 3 RCTs MTX appears to be more effective than GCs alone in reducing relapses and exposure to GCs only after 24-26 weeks of treatment, thus showing that there is probably a latency period before MTX exerts its pharmacologic action.[11] Overall, MTX has a small and late steroid-sparing effect without reducing the incidence of steroid-related side effects. According to 2018 Update of EULAR recommendations, which are intended to provide advice on the management of LVV to clinicians,[12] isolated GCs represent the cornerstone of GCA treatment. However, in patients with refractory or relapsing disease or at high risk of developing GC-related side effects, MTX should be added to GCs as a second choice.

There are no RCTs on the usefulness of *leflunomide* (LEF) as a steroid-sparing agent in GCA. Two retrospective studies reported that LEF can be effective and safe in managing this LVV.[13,14] Besides, in a prospective observational study most of the patients treated with LEF (56.7%) in addition to GCs were withdrawn from GCs at week 48 from the beginning of therapy, while none in GCs-only group was able to discontinue GCs.[15] Given the design and the relatively small number of patients described in these studies, LEF is not among the recommended drugs which can be added to GCs in refractory/relapsing patients with GCA.[12]

No high-quality evidence support the efficacy of *cyclosporine* (CysA) or *azathioprine* (AZA) as steroid-sparing agents in newly diagnosed and relapsing patients with GCA.[16] Indeed, after 6 months of therapy no statistically significant difference was seen in the cumulative GC dose between patients treated with a combined regimen (GCs + CysA) and those treated with GCs alone (1.41 g *versus* 1.44 g, respectively).[17] The lack of a steroid-sparing effect with CysA was confirmed in an open-label, randomized controlled trial published some years later by the same group.[18] Moreover, most of the 29 patients who received CysA developed side effects, such as new onset hypertension or increase in creatinine levels. Lastly, the results of a trial aimed at exploring the effectiveness of AZA were hampered by methodological issues, thus not allowing to draw definitive conclusions about the role of this drug as a steroid-sparing agent in GCA.[19]

Role of biological immunosuppressive drugs

Since biological immunosuppressive drugs (bDMARDs) were discovered, some trials have investigated their effectiveness in GCA patients. Indeed, it is well known that cytokines, particularly IL-6, but also TNF-alpha may play a pivotal role in the etiopathogenesis of GCA, thus representing potential targets for bDMARDs.[20,21]

IL-6 is a key driver in GCA etiopathogenesis. Levels of IL-6 correlate well with disease activity.[22] Besides, it is noteworthy that subjects with persistently elevated IL-6 levels are at higher risk of relapse/recurrence of GCA, despite proper GC therapy.[23] Lastly, high expression of IL-6 has been found in the arterial wall of patients with inflamed temporal arteries.[20] The pivotal role of the IL-6 pathway in the pathogenesis of GCA makes *tocilizumab* (TCZ) an attractive therapeutic option for GCA, given its ability to inhibit IL-6. Some case reports and observational studies suggested that TCZ was effective in treating GCA.[24,25] Two subsequent RCTs have confirmed its effectiveness. The first RCT was published in 2016.[26] This study enrolled 30 patients diagnosed with GCA according to 1990 American College of Rheumatology (ACR) criteria for the classification of GCA. Among them, 20 subjects received intravenous TCZ (8 mg/kg/4 weeks) in addition to GCs, while the remaining 10 patients received placebo and GCs. Eighty-five% of patients who received TCZ achieved the primary outcome (complete remission by week 12 at a prednisolone dose of 0.1 mg/kg per day). Moreover, 85% of subjects treated with TCZ experienced a relapse-free survival by week 52, with a statistically significant difference compared with the placebo arm (risk difference 65%, P=0.001). The cumulative prednisolone dose after 52 weeks was significantly lower in TCZ group compared to placebo (43 mg/kg *vs* 110 mg/kg, P=0.0005). TCZ-treated patients received less than half the cumulative GC dose of patients treated with placebo. No safety concerns in the TCZ group arose from this trial.[26]

The Trial of Tocilizumab in Giant Cell Arteritis Actemra (GiACTA) published in 2017 had the aim to evaluate the efficacy and safety of TCZ in patients with newly diagnosed or recurrent GCA. This study included 251 subjects in 14 countries. Patients were randomly assigned with a 2:1:1:1 ratio to receive subcutaneous TCZ (at a dose of 162 mg) weekly or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. TCZ, administered weekly or every other week, combined with a 26-week prednisone taper was superior to either 26-week or 52-week prednisone tapering plus placebo with regard to sustained GC-free remission in patients with GCA, which was the primary endpoint of the trial. Indeed, 56% of subjects treated with TCZ every week and 53% of those in treatment with TCZ every other week achieved a sustained remission at week 52. Conversely, this outcome was reached only by 18% of subjects who received the placebo and had a 52-week prednisone taper and by 14% of patients who received the placebo and the 26-week prednisone taper. TCZ also had a powerful steroid-sparing effect in TCZ-treated patients receiving about half the cumulative dose of patients treated with GCs only. As to safety concerns, serious adverse events were similar across the four groups. In particular, no deaths, nor bowel perforations were reported.[27]

In light of the encouraging results from these studies, according to EULAR recommendations,[12] TCZ should be added to GCs as a first choice in patients with a refractory or relapsing GCA or at high risk of GC-related adverse events or complications. However, it is still unknown which patients could benefit from TCZ and whether this bDMARD should be used for all newly diagnosed GCA patients or only for patients at high risk of developing serious GCs side effects or for subjects with a relapsing disease. An open question concerns the optimal duration of the treatment with TCZ, which still needs to be defined. The last point to consider is whether the maintenance treatment with a conventional immunosuppressive drug should be started once disease remission has been obtained with TCZ to maintain the remission after the discontinuation of TCZ.[28]

In a small RCT which included 44 newly diagnosed GCA patients treated with GCs as induction therapy, *infliximab* (IFX) did not show superiority over GCs alone in reducing the number of relapses. Moreover, IFX had no steroid-sparing effect, while it increased the incidence of infections compared to GCs only.[29] Similarly, the role of *adalimumab* (ADA) as a steroid-sparing agent was evaluated, too. A double-blind, multicenter controlled study by Seror *et al.,* which enrolled 70 patients newly diagnosed with GCA, failed to achieve the primary endpoint, since the 34 patients who received ADA in addition to a standardized GC therapy were not able to taper more rapidly GCs compared with the placebo arm.[30] However, a GC-sparing effect for IFX and ADA may not be completely excluded, since the reliability of the results of the studies

mentioned above could have been affected by the limited number of patients enrolled.

Etanercept (ETN) seems to show a small steroid-sparing effect in GCA patients with GC-related side effects, as demonstrated in a double-blind placebo-controlled trial. Even in this case, the small number of patients included did not allow to draw definitive conclusions.[31]

Abatacept (ABA) is a recombinant fusion protein which modulates CD28-mediated T-cell costimulation. The Vasculitis Clinical Research Consortium assessed the efficacy of ABA in managing newly diagnosed or relapsing GCA patients treated with GCs in a RCT. The relapse-free survival rate at 12 months (primary endpoint) was 48% for those receiving abatacept and 31% for those receiving placebo. The difference was statistically significant (P=0.049).[32] Therefore, in patients with GCA, the addition of ABA to a treatment regimen with GCs may mildly reduce the risk of relapse.

The role of *ustekinumab* (UST) as a blocker of IL-12/23 inflammatory pathway in GCA was evaluated in a prospective open-label study by Conway *et al*. A total of 25 patients with refractory GCA received subcutaneously UST 90 mg every 12 weeks. A statistically significant difference between week 0 and week 52 of treatment was found in the median daily prednisolone dose and in C-reactive protein (CRP) levels, which decreased considerably. Besides, 24% of subjects were able to discontinue GCs completely and no patients experienced a GCA relapse during UST treatment.[33]

In summary, anti-TNF-alpha agents are not useful in managing GCA and the role of ABA and UST has not been well defined yet.

All the immunosuppressive drugs investigated in RTCs and used in GCA are summarized in Table 1. Due to the low quality of the trials, those on AZA and CysA were not included in the Table.

Role of other biological immunosuppressive drugs and small molecules

Presently, the introduction of other drugs, with different mechanisms of action, routes and frequency of administration such as *rituximab* (RTX), *anakinra, gevokizumab* and, more recently, *Janus kinasis inhibitors* (JAKi), has shed light on the possibility of using alternative molecules which could play a pivotal role in blocking inflammatory cascade. More in detail, tofacitinib has shown to modulate innate and adaptive immunity in vessel wall in an animal model.[34] One phase 2 trial of baricitinib (NCT03026504) and one phase 3 trial of upadacitinib (NCT03725202) in patients with relapsing GCA are currently ongoing.

Management of Takayasu arteritis

Role of glucocorticoids

GCs represent the mainstay for TAK treatment. However, about 80% of TAK patients have a progressive or relapsing/remitting disease. Serial angiographic evaluations have shown that new lesions can be found in 61% of patients, even when the arteritis is thought to be in remission and relapses and anatomic progression usually occur after steroid tapering.[35] Since in TAK vasculitis patients are commonly young women and the disease is often progressive, there is the need to introduce drugs with a powerful steroid-sparing effect in order to minimize GCs exposure.

Role of non-biological immunosuppressive drugs

RCTs on the role of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in TAK are still lacking. Hoffman *et al.* found that weekly low-dose *MTX* was able to induce disease remission and reduce GCs exposure in most patients with a persistent or GC-refractory TAK.[36] *AZA* (2 mg/kg/day) in addition to GCs (1 mg/kg/day) was effective in managing symptoms, improving laboratory findings and halting angiographic progression in TAK after 12 months of treatment.[37] In an open-label long-term longitudinal study by de Souza *et al.*, which enrolled 12 patients, sustained remission was achieved in approximately half of patients after 12 months of therapy with *LEF*. There were no safety concerns with this drug.[38] The role of *mycophenolate mofetil* (MMF) in TAK was addressed in a meta-analysis conducted by Dai *et al.* in 2017. Their main finding was that MMF could be used as an effective drug to control disease activity and taper the GC dosage.[39] One study had the aim to assess the efficacy and safety of two csDMARDs (*cyclophosphamide*, *CYC*, on one hand and MTX on the other hand) in TAK arteritis. The authors found that there was no statistically significant difference in clinical remission rates between CYC and MTX, even if magnetic resonance angiography (MRA) revealed a significant radiologic improvement, particularly in wall enhancement scores, in the CYC group, but not in the MTX one. Besides, no serious side effects were reported in CYC group.[40]

In summary, in TAK patients EULAR recommendations support upfront introduction of csDMARDs together with GCs, since immunosuppressive agents seem to be effective in halting disease progression, preventing future relapses and reducing GC-related morbidity, despite the low-quality evidence coming from mainly observational cohort studies.[12]

Role of biological immunosuppressive drugs

Since TNF-alpha is implicated in the formation of granulomas and in TAK arteritis granulomatous inflammation is seen, *anti-TNF-alpha agents* represent attractive therapeutic options in this LVV.

The role of ETN and IFX in TAK was addressed in an open-label pilot study including 15 patients with TAK refractory to GCs alone or associated to other immunosuppressive drugs (MTX, CYC, MMF, AZA, CysA or tacrolimus). Ten out of 15 subjects reached complete remission and were able to discontinue steroid therapy. Four patients achieved a partial remission, without stopping GCs.[41] A study of Molloy *et al.* confirmed the efficacy of anti-TNF-alpha agents. Twenty-five subjects with TAK refractory to traditional immunosuppressants were treated with IFX and/or ETN for up to 7 years. Sixty% of subjects were able to reach remission and to suspend GCs.[42] Similarly, Schmidt *et al*. found that 90% of patients with refractory TAK in treatment with IFX, ETN or ADA reached remission, which was sustained in 50% of cases. Besides, only a minority of subjects experienced a relapse during the anti-TNF-alpha therapy.[43] Overall, among 120 patients treated with anti-TNF-alpha, around 90% responded to treatment and a minority developed relapses (37%) or adverse events (18%) during the therapy.[44] Gudbrandsson *et al.* compared in a population-based study from South-East Norway anti-TNF-alpha therapy (27 patients in IFX, 5 in ETN) and csDMARDs. Patients on TNF inhibitors had a higher sustained remission rate than patients on csDMARDs (42% *vs* 20%; P=0.03).[45]

Since plasmablasts are increased in peripheral blood of patients with TAK and their levels correlate with disease activity,[46] *RTX* appears to be a good option in treating TAK refractory to conventional therapies. A retrospective study was conducted by Pazzola *et al.* on the efficacy of RTX on 7 patients with TAK not responsive to high doses of GCs and csDMARDs and/or anti-TNF-alpha agents. The authors found conflicting results, since, after RTX treatment, 4 out of 7 patients showed a persistently active disease, while the remain-

Table 1. Immunosuppressive drugs investigated with randomized controlled trials in Giant cell arteritis (due to the low quality of the trials, those on azathioprine and cyclosporine were not included in the Table).

Drug	Dosage	Study ID	Study design	N	Intervention arm	Control arm	Outcomes	Outcome measures	Results (i)	Results (c)	Side effects
MTX	10 mg/week	Jover *et al.*[8]	Randomized, double-blind, placebo-controlled trial	42 21 (i) vs 21 (c)	PRED p.o. (60 mg/day) + MTX p.o. (10 mg/week)	PRED + placebo	Safety and efficacy of combined therapy with PRED + MTX	Number of relapses Cumulative PRED dose (mg)	9 (45%) 4187±1529	16 (84.2%) 5489.5±1396	Comparable between the groups
MTX	Up to 15 mg/week	Hoffman *et al.*[9]	Randomized, double-blind, placebo-controlled trial	98 51 (i) vs 47 (c)	PRED p.o. (1 mg/kg/day) + MTX p.o. (up to 15 mg/week)	PRED + placebo	Efficacy of combined therapy with PRED + MTX	First disease relapse (12 months) Number of treatment failures (12 months)	31 (74.8%) 22 (57.5%)	31 (91.3%) 24 (77.3%)	Comparable between the groups
MTX	7.5 mg/week	Spiera *et al.*[10]	Randomized, double-blind, placebo-controlled trial	21 12 (i) vs 9 (c)	PRED p.o. (1 mg/kg/day) + MTX p.o. (7.5 mg/week) when PRED dose of 30 mg/day	PRED + placebo	Efficacy of MTX in disease-controlling and in GCs-sparing	Cumulative PRED dose (mg) Number of weeks to completion of GCs Weeks to taper PRED to less than 10 mg PRED/day	6469±2024 68 23	5908±2131 60 25	Comparable between the groups
TCZ	8 mg/kg/4 weeks	Villiger *et al.*[26]	Phase 2, randomized, double-blind, placebo-controlled trial	30 20 (i) vs 10 (c)	PREDNL p.o. (1 mg/kg) + TCZ i.v. (8 mg/kg/4 weeks)	Placebo	Efficacy and safety of TCZ	Proportion of patients who achieved complete remission at a PREDNL dose of 0.1 mg/kg/day (week 12) Proportion of patients who achieved relapse-free survival (week 52) Cumulative PREDNL dose (mg/kg) after 52 weeks	17 (85%) 17 (85%) 43 (39 to 52)	4 (40%) 2 (20%) 110 (88 to 150)	Comparable between the groups 7 severe adverse events in 7 patients (i) vs 10 severe adverse events in 5 patients (c)
TCZ	162 mg/week 162 mg/2 weeks	Stone *et al.*[27]	Randomized, double-blind, placebo-controlled trial	251 100 (i1); 50 (i2); 50 (c1); 51 (c2)	TCZ s.c. (162 mg/week) + 26-week GC taper p.o. (i1) TCZ s.c (162 mg/2 weeks) + 26-week GC taper p.o. (i2)	Placebo + 26-week GC taper p.o. (c1) Placebo + 52-week GC taper p.o. (c2)	Superiority of TCZ over placebo in inducing sustained GC-free remission	Rate of participants in sustained GC-free remission at week 52 vs placebo + 26-week GC taper Percentages of patients who had a flare (at week 52) Cumulative PRED dose (mg) over the 52-week trial period	56% (i1) 53% (i2) 23% (i1) 26% (i2) 1862 (i1) 1862 (i2)	14% (c1) 18% (c2) 68% (c1) 49% (c2) 3296 (c1) 3818 (c2)	Comparable between the groups Percentages of patients with ≥1 serious adverse event: 15% (i1); 14% (i2); 22% (c1); 25% (c2)
IFX	5 mg/kg/8 weeks	Hoffman *et al.*[29]	Randomized, double-blind, placebo-controlled trial	44 28 (i) vs 16 (c)	IFX i.v. (5 mg/kg) at weeks 0, 2, 6, then every 8 weeks + GCs p.o.	Placebo + GCs	Efficacy and safety of IFX in maintaining GC-induced remission	Proportion of relapse-free patients through week 22 Proportion of patients with GCs dosages tapered to 10 mg/day without relapse Cumulative PRED dose (mg) at week 22	12 (43%) 17 (61%) 3154.10	8 (50%) 12 (75%) 3049.56	Comparable between the groups 3 patients (11%) reported serious infections in the IFX group vs 1 (6%) in the placebo group
ETN	25 mg/twice week	Martínez-Taboada *et al.*[31]	Randomized, double-blind, placebo-controlled trial	17 8 (i) vs 9 (c)	ETN s.c. (25 mg/twice week) + PRED p.o. (≥10 mg/day)	Placebo + PRED p.o. (≥10 mg/day)	Efficacy and safety of ETN	Proportion of patients able to discontinue the GC therapy and control disease activity (12 months) Cumulative PRED dose (g) at 12 months Proportion of patients who relapsed during the active phase of the study	50% 1.5 50%	22.2% 3 77.8%	Comparable between the groups 2 patients (25%) reported serious adverse events in the ETN group vs 2 (22.2%) in the placebo group

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Table 1. Continued from previous page.

Drug	Dosage	Study ID	Study design	N	Intervention arm	Control arm	Outcomes	Outcome measures	Results (i)	Results (c)	Side effects
ADA	40 mg/2 weeks	Seror *et al.*[30]	Randomized, double-blind, placebo-controlled trial	70 34 (i) vs 36 (c)	ADA s.c. (40 mg/2 weeks) + PRED p.o. (0.7 mg/kg/day)	Placebo + PRED p.o. (0.7 mg/kg/day)	Efficacy and safety of ADA	Percentage of patients in remission with less than 0.1 mg/kg/day of PRED at week 26 Mean PRED daily dose at week 26 (mg/kg) Median time to first relapse	20 (58.9%) 0.12 mg/kg±0.05 24 weeks (95% CI 17 to 31)	18 (50%) 0.13 mg/kg±0.07 17 weeks (95% CI 11 to 29)	24 patients (70.59%) in intervention arm experienced at least one adverse event compared to 35 (97.22%) in the placebo group Serious adverse events occurred in 5 patients (14.71%) in intervention arm compared to 17 (47.2%) in the placebo group
ABA	10 mg/kg/4 weeks	Langford *et al.*[32]	Randomized, double-blind, placebo-controlled trial	41 20 (i) vs 21 (c)	ABA i.v. (10 mg/kg on day 1, 15, 29 and weeks 8) + GC 40-60 mg/day with 28-week taper p.o.	Placebo + GC 40-60 mg/day with 28-week taper p.o.	Efficacy and safety of ABA	Proportion of patients who achieved relapse-free survival after 12 months Median duration of remission (months)	48% 9.9	31% 3.9	Comparable between the groups Serious adverse events occurred in 10 patients in ABA group compared to 8 in the placebo group

ABA, abatacept; ADA, adalimumab; AZA, azathioprine; c, control arm; c1, control arm 1; c2, control arm 2; ETN, etanercept; GC, glucocorticoids; i, intervention arm; i1, intervention arm 1; i2, intervention arm 2; IFX, infliximab; i.v., intravenous route; MTX, methotrexate; p.o., oral route; PRED, prednisone; PREDNL, prednisolone; s.c., subcutaneous route; TCZ, tocilizumab.

ing 3 subjects who received RTX as rescue therapy reached complete remission. However, the number of patients included in this study was too small to draw definitive conclusions.[47]

On the basis of a rationale similar to that of GCA, IL-6 blockade with *TCZ* may represent an attractive therapeutic option also for TAK. The role of TCZ in relapsing TAK was assessed in a RCT by Nakaoka *et al.* (the TAKT study). This study included 36 patients with TAK who had relapsed within the last 12 weeks, while treated with at least 0.2 mg/kg/day prednisolone equivalent. They were randomly assigned, in a 1:1 ratio, to receive weekly subcutaneous TCZ at a dosage of 162 mg or placebo. Patients had to reach remission with oral GCs within one week before randomization. GC dose was tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day. The primary outcome (time to first relapse of TAK per protocol-defined criteria in the intent-to-treat group) was not achieved and only a trend toward significance was observed. However, although the primary endpoint was not met, the results were in favor of TCZ over placebo and indicated the need of larger studies to evaluate the efficacy of TCZ in TAK.[48] Evidence on TCZ efficacy came from a French study conducted on 46 subjects, most of whom with a refractory disease. After TCZ administration, the authors observed a significant decrease in the median National Institute of Health (NIH) scale and in the daily prednisone dose. Finally, the authors also observed a decrease in radiological activity from 83% to 17% after 12 months of therapy. This study demonstrated the efficacy of TCZ in reducing disease activity and in saving GCs in refractory TAK.[49]

A RCT showed that the addition of *ABA* to GCs did not reduce the risk of relapse in patients with TAK.[50] In a pilot study 40 mg of *UST* were administered to 3 patients with refractory TAK at day 0 and at day 28. Inflammatory markers decreased at day 84, but vascular wall enhancement at MRA still remained.[51]

In summary, even though RCTs on anti-TNF-alpha agents are lacking, they can be useful in treating TAK in clinical practice. TCZ was favored over placebo in time to first relapse, despite this result did not reach a statistically significant difference, probably because of the small number of patients enrolled in the study. Therefore, according to EULAR recommendations, anti-TNF-alpha agents or TCZ should be considered as a second-line therapy when a csDMARD has failed in inducing remission or in cases of relapsing disease.[12] As shown by RCT results, ABA is not effective in managing TAK. Experience with RTX and UST is too limited to draw definitive conclusions.

All the immunosuppressive drugs investigated with RTCs and used in TAK are shown in Table 2.

Role of small molecules

Lastly, there are two ongoing studies (NCT04299971; NCT04161898) addressing the potential role of *JAKi* in blocking cytokine signaling dependent on JAK3 and JAK1 in TAK.

Revascularization procedures

It is not uncommon for patients with TAK to undergo *surgical interventions*. The endovascular ones mainly encompass percutaneous transluminal angioplasty (PTA) and stent placement, while open surgery involves bypass grafting, endarterectomy and patch angioplasty. Outcomes of endovascular interventions were compared to those of open surgery in a meta-analysis. Endovascular procedures seemed to be burdened by a higher risk of restenosis. There were no differences in terms of mortality rates between the two groups.[52] Restenosis is a common complication, being reported in 17-60% of patients treated with surgical interventions (stenting

Table 2. Immunosuppressive drugs investigated with randomized controlled trials in Takayasu arteritis.

Drug	Dosage	Study ID	Study design	N	Intervention arm	Control arm	Outcomes	Outcome measures	Results (i)	Results (c)	Side effects
TCZ	162 mg/week	Nakaoka *et al.*[48]	Randomized, double-blind, placebo-controlled trial	36 18 (i) vs 18 (c)	GCs p.o. (at least 0.2 mg/kg/day) + TCZ s.c. 162 mg/week	GCs p.o. + placebo	Efficacy and safety of TCZ	Time to relapse of TAK (protocol-defined criteria) Time to relapse of TAK (Kerr's definition) Time to relapse of TAK (clinical definition)	HR 0.41 (95%CI 0.15 – 1.1) HR 0.41 (95%CI 0.15 – 1.10) HR 0.70 (95%CI 0.29 – 1.70)		Comparable between the groups Serious adverse events were reported in one TCZ-treated and two placebo-treated patients
ABA	10 mg/kg/4 weeks	Langford *et al.*[50]	Randomized, double-blind, placebo-controlled trial	26 15 (i) vs 11 (c)	ABA i.v. 10 mg/kg on days 1, 15 and 29 and week 8 + PRED p.o. 40-60 mg/day followed by a tapering schedule. From week 12, if patients in remission → continue ABA/4 weeks i.v.	ABA i.v. 10 mg/kg on days 1, 15 and 29 and week 8 + PRED p.o. 40–60 mg/day followed by a tapering schedule. From week 12, if patients in remission → continue GCs + placebo	Efficacy and safety of ABA	Relapse-free survival rate at 12 months Median duration of remission (months)	22% 5.5	40% 5.7	Comparable between the groups 12 serious adverse events were reported in ABA-treated arm, while 9 serious adverse events occurred in the placebo one

ABA, abatacept; c, control arm; GC, glucocorticoids; i, intervention arm; i.v., intravenous route; p.o., oral route; PRED, prednisone; s.c., subcutaneous route; TCZ, tocilizumab.

procedures, above all).[49,50] A meta-analysis showed no significant differences in the risk of restenosis when comparing PTA and stenting procedures.[53] The only exception was renal arteries, in which balloon angioplasty yielded better results than stenting [odds ratio (OR)=4.40, 95% confidence interval (CI)=2.14-9.02, P<0.001], although burdened by a greater risk of vascular complications (OR=0.07, 95% CI=0.02-0.29, P<0.001). EULAR expert panel recommends that endovascular interventions or reconstructive surgery should be performed when TAK is in stable remission, except for vessel dissection or critical ischemia which should be referred to vascular surgeon as a matter of urgency.[12]

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