Era of steroid sparing in the management of immune-mediated inflammatory diseases

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ABSTRACT
Glucocorticoids (GCs) have played a pivotal role in the treatment of immune-mediated inflammatory diseases (IMIDs) for a long time. However, GCs also incur a significant risk of undesirable adverse events such as Cushingoid changes, osteoporosis, glaucoma and metabolic abnormalities such as diabetes and hypercholesterolemia, which may lead to life-threatening cerebrovascular and cardiovascular events. High-dose GCs may also cause mental disorders and osteonecrosis. Recently, new therapeutic strategies have been developed to reduce the dose or even eliminate the need for GCs; multi-target drug therapies for systemic lupus erythematosus (SLE), biological agents such as tocilizumab and rituximab for systemic vasculitis, and anakinra and tocilizumab for adult-onset Still’s disease. Therefore, the era of GC-sparing or GC-free treatment for IMIDs is on the horizon.

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1. Introduction
Glucocorticoids (GCs) have played a pivotal role in the treatment of systemic inflammatory diseases for a long time, and remain the first-line treatment for systemic lupus erythematosus (SLE), inflammatory myositis and systemic vasculitis [1]. However, GCs also incur a significant risk of undesirable adverse events (AE) like Cushingoid changes, osteoporosis, glaucoma and metabolic abnormalities such as diabetes and hypercholesterolemia, which may lead to life-threatening cerebrovascular and cardiovascular events [1,2]. In addition, high-dose GCs can also cause mental disorders and osteonecrosis. Molecular and cellular understanding of systemic inflammatory diseases can provide clues for developing innovative treatments and strategies. Among human diseases, such as cancers, infections and metabolic diseases, there is a group of inflammatory diseases mediated by immunological mechanisms without apparent etiologies, called immune-mediated inflammatory diseases (IMIDs) including SLE, rheumatoid arthritis (RA), psoriatic arthritis and systemic vasculitis [3,4]. While the human immune system involves highly complex and coordinated processes, it has been demonstrated that cytokines are overexpressed and T- and B-cells are accumulated in affected tissues in IMIDs [3,4]. These key players have been postulated as potential targets for therapeutic intervention. Indeed, novel therapeutic antibodies targeted against single molecules that are intimately associated with disease pathogenesis have led to significantly better outcomes in clinical practice [5–7]. As a result, the treatment of several IMIDs, such as RA and psoriatic arthritis, does not necessitate long-term steroid treatment [8–10]. Recently, several new therapeutic strategies for the treatment of other IMIDs have been developed to reduce the dose of steroids or even eliminate the need for steroid therapy. This review describes these new therapeutic agents and strategies in the treatment of IMIDs.

2. Systemic lupus erythematosus
Systemic lupus erythematosus is a prototype autoimmune disease with a wide spectrum of clinical manifestations [11]. While abundant production of autoantibodies and subsequent formation of immune complexes lead to tissue damage such as in glomerulonephritis, T and B cells play a crucial role in the pathogenesis of SLE. Additionally, comprehensive mRNA expression analysis has revealed that Type I interferon-related genes are up-regulated in peripheral blood cells, in part through the increased production of interferon [11]. Various immunosuppressants have been developed to reduce the amount of steroid. The guideline by the American College of Rheumatology, European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (ACR EULAR/ERA-EDTA) suggests that...
remission induction therapy for class III or IV lupus nephritis (LN) should include GCs and either cyclophosphamide (CYC) or mycophenolate mofetil (MMF) [12,13]. However, the complete remission rate for LN with current induction treatment regimens remain inadequate (5.8–56.2%) [14,15].

According to the abovementioned mechanisms, various drugs have been trialed for LN. Belimumab, a monoclonal antibody against B-cell activating factor/B-lymphocyte stimulator (Blys), was found to be effective for reducing flares, disease severity and proteinuria in SLE patients [16]. In contrast, rituximab, a chimeric monoclonal antibody to CD20, was not found to be more effective than standard care with immunosuppressive agents as first-line therapy, although it may be efficacious for the treatment of patients with refractory disease [16]. Current trials of abatacept, a soluble Fc:CTLA-4 fusion protein that competes with CD28 to prevent T-cell activation, combined with MMF and GCs suggest that it is ineffective for LN [17]. Studies have also examined the effectiveness of anti-interferon alpha agents [18]. The findings suggest that combination therapies with one immunosuppressant and GC may be insufficient to reduce the required steroid dosage because of the heterogeneous pathogenesis of SLE, which consists of various aberrant immunological mechanisms. Therefore, multi-targeted drug therapy approaches attempting to target different aspects of inflammation implicated in LN have been performed. Bao et al. [19] first reported in 2008 that tacrolimus plus MMF could achieve a higher complete remission rate within 24 weeks than CYC (50% vs. 5%, p < .05) [19] in the treatment of mixed diffuse proliferative and membranous LN (class III or IV + V). Recently, we reported a prospective, open-label, single-center, pilot study of a multi-target therapy comprising CYC and tacrolimus [20]. In this study prednisolone (PSL) was started at a dose of 0.6–1.0 mg/kg/day for 2 weeks and 500 mg of intravenous CYC was administered biweekly for 3 months (six times) with 3 mg/day of tacrolimus daily. This combination therapy was more effective (80% complete remission rate) than our historical control conventional CYC therapy at month 6 (38.9% complete remission rate) using intention-to-treat analysis (Figure 1) [21].

| Remission rate at 6 months | Remission rate at 12 months |
|-----------------------------|-----------------------------|
| CYC+TAC: 80.0% | CYC: 38.9% |
| 3 | 12 |
| 11 | 7 |
| p=0.020 | |
| | CYC+TAC: 80.0% | CYC: 44.4% |
| 3 | 10 |
| 12 | 8 |
| p=0.041 | |

**Figure 1.** (A) Outcomes at 6 months for lupus nephritis treated with CYC + TAC versus CYC alone. (B) Outcomes at 12 months for lupus nephritis treated with CYC + TAC versus CYC alone. Fisher’s exact test was used to examine the differences between the two groups. (C) Probability of CR of lupus nephritis treated with CYC + TAC versus CYC alone. Kaplan–Meier curves were plotted for time-to-event of CR in the group of CYC + TAC (n = 15) and CYC (n = 18), and discontinuations to follow-up were accounted for by censoring, which appeared as a data point on a flat part of the curve. The differences between two curves were analyzed using the log-rank test (p = .021). CYC: cyclophosphamide; TAC: tacrolimus; CR: complete remission.
In 2013, a rituxilup trial showed the possibility of eliminating the need for daily oral GCs in the management of LN for the first time in history [22]. These formed the first step for future treatment strategies for LN.

3. Giant cell arteritis/Takayasu arteritis & polymyalgia rheumatica

Large-vessel vasculitis (LVV), which includes giant cell arteritis (GCA) and Takayasu arteritis (TAK), affects the aorta and its branches. While GCA and TAK share similar clinical, radiographical and histopathological features, they have important differences such as age of onset and sex differences [23]. Polymyalgia rheumatica (PMR) is a common inflammatory disease that affects the elderly and is frequently associated with GCA and may be part of the same disease spectrum [24]. Steroid therapy has been the mainstay of therapies for GCA, TAK and PMR. However, reducing the dose of steroids has resulted in relapses, and prolonged GC therapy is frequently associated with various significant morbidities [25,26]. Conventional immunosuppressants such as methotrexate, leflunomide and CYC have modest steroid-sparing effects, leaving an urgent unmet need. The advent of biological therapies has increased interest in targeted therapies.

Recently, a review article was published on the efficacy of biologics in the treatment of LVV and PMR (Table 1) [27]. It reported that while antitumor necrosis factor (TNF) therapy may be beneficial for patients with TAK, abatacept is ineffective for reducing TAK flares. Among the biologics reviewed, tocilizumab (TCZ) appeared to be the most effective for these diseases. In a phase 2, double-blind, placebo-controlled trial, 30 patients with GCA were randomized to TCZ 8 mg/kg i.v. (cebo-controlled trial, 30 patients with GCA were for these diseases. In a phase 2, double-blind, placebo-controlled trial, 30 patients with GCA were randomized to 162 mg s.c. weekly or 26 week PSL-taper and TCZ 162 mg s.c. every other week. The primary endpoint was the proportion of patients in sustained remission (weeks 12–52). Sustained remission occurred in 56.0% of patients in the TCZ-weekly arm and 53.1% in the TCZ-every-other-week arm, compared to 14.0% in the placebo 26 week PSL-taper and 17.6% in placebo 52 week PSL-taper arms (p < .001 for comparisons of active treatment vs. placebo at each time point). The cumulative median PSL dose over 52 weeks was 1862 mg in each of the TCZ groups compared to 3296 mg in the placebo 26 week PSL-taper group (p < .0001) and 3818 mg in the placebo 52 week PSL-taper group (p < .0003). Serious AEs and serious infectious AEs were not more frequent in the TCZ groups than the placebo groups [29].

A phase 3, double-blind, placebo-controlled trial for TAK was conducted in Japan in 2017 [30]. Thirty-six TAK patients who had relapsed within the previous 12 weeks and were induced into remission with oral GC therapy were randomly assigned 1:1 to receive weekly TCZ 162 mg (n = 18) or placebo subcutaneously (n = 18). Concomitant oral GC was tapered by 10% weekly from week 4 to a minimum of 0.1 mg/kg/day. Although the primary endpoint of time to first relapse was not significantly different between the two groups (hazard ratio 0.41 (95%CI 0.15, 1.10), based on relapse in 8 (44.4%) TCZ-treated and 11 (61.1%) placebo-treated patients], TCZ might have a beneficial effect on each of the signs and symptoms of relapse. This clinical study led to the approval of TCZ for LVV in Japan in August 2017.

In an open-label trial, 20 newly diagnosed GC-naïve patients with PMR were treated with three infusions of TCZ 8 mg/kg, followed by GC therapy (0.15 or 0.3 mg/kg) from week 12. PMR activity scores decreased significantly and all patients were able to start low-dose PSL (0.15 mg/kg) at week 12 [31]. In another phase 2 study, 10 patients with new PMR were treated with TCZ 8 mg/kg i.v. for 1 year with rapid tapering of GCs. One withdrew at 2 months but the remaining nine patients were able to discontinue GCs at 4 months and were relapse-free at 15 months. Adverse effects were observed in 22 events, none of which were considered serious, and included upper respiratory tract infection [32]. Therefore, GC-sparing by TCZ may be an effective

### Table 1. Summary of targeted biological therapies and their findings in LVV and PMR.

|           | PMR | GCA | TAK |
|-----------|-----|-----|-----|
| Anti-TNF therapy | Δ   | Δ   | O   |
| Tocilizumab     | O   | O   | O   |
| Abatacept       | –   | –   | X   |
| IL-1 antagonist  | O   | –   | –   |
| Ustekinumab     | –   | –   | –   |
| Secukinumab     | O   | –   | –   |

*Δ: benefit; "possible benefit; “some benefit or controversial; “no benefit; not evaluated. PMR: polymyalgia rheumatic; GCA: giant cell arteritis; TAK: Takayasu disease.

Frequency of AEs was similar between the regimen groups: 15 patients (75%), 26 events, 7 serious AEs in the TCZ group and 7 patients (70%), 23 events, 10 serious AEs in the placebo group. A large, multicenter, phase 3 randomized controlled trial (GiACTA) was completed in 2017 [29]. In this trial, 251 patients were randomized to four groups: 26 week PSL-taper and placebo, 52 week PSL-taper and placebo, 26 week PSL-taper and TCZ 162 mg s.c. weekly or 26 week PSL-taper and TCZ 162 mg s.c. every other week. The primary endpoint was the proportion of patients in sustained remission (weeks 12–52). Sustained remission occurred in 56.0% of patients in the TCZ-weekly arm and 53.1% in the TCZ-every-other-week arm, compared to 14.0% in the placebo 26 week PSL-taper and 17.6% in placebo 52 week PSL-taper arms (p < .001 for comparisons of active treatment vs. placebo at each time point). The cumulative median PSL dose over 52 weeks was 1862 mg in each of the TCZ groups compared to 3296 mg in the placebo 26 week PSL-taper group (p < .0001) and 3818 mg in the placebo 52 week PSL-taper group (p < .0003). Serious AEs and serious infectious AEs were not more frequent in the TCZ groups than the placebo groups [29].
therapeutic strategy for elderly PMR patients with co-morbidities such as osteoporosis and diabetes [33].

4. ANCA-associated vasculitis

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a multisystem autoimmune syndrome predominantly affecting microscopic vessels. It is characterized by pauci-immune glomerulonephritis and circulating autoantibodies against neutrophil cytoplasmic antigens, including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). GPA and MPA are regarded under the same spectrum, while EGPA has slightly different pathophysiology. Combined treatment with CYC plus GC has been the standard therapy for remission induction of AAV for nearly four decades and is effective in 70% to 90% of patients [34]. However, in addition to the adverse effects of GC, CYC is associated with risks of infertility, cytopenia, infection, bladder injury and cancer. Moreover, higher rates of death are related to adverse events rather than active vasculitis in AAV patients in the first year of therapy [35]. Recently, the remission rate of rituximab-based regimens was shown not to be inferior to that of standard intravenous CYC as induction therapy in AAV [36]; therefore, rituximab is emerging as the standard therapy for avoiding adverse drug reactions resulting from CYC or for treating patients who are refractory to CYC. As maintenance therapy, rituximab is more effective than azathioprine [37]. Several reports have suggested TCZ as a potential treatment for AAV as well as LVV [38]. The use of concomitant GC is a significant risk factor for developing serious infections during TCZ treatment [39]. Therefore, based on our experience that TCZ monotherapy without GC and CYC led to the successfully remission of a patient with AAV complicated with RA, we conducted a prospective single-arm, single-center, cohort, pilot study on the efficacy of TCZ monotherapy for 7 MPA patients [40]. All patients received 8 mg/kg of intravenous TCZ biweekly for the first 2 months (5 courses), and monthly for the next 10 months (10 courses). After 1 year of TCZ monotherapy, the patients were followed-up without any treatment for another year. Complete remission, defined by a Birmingham Vasculitis Activity Score of 0 at 2 consecutive visits, was achieved in two patients at 6 months and three patients at 12 months. Two patients were withdrawn from the trial: one because of inefficacy at 6 weeks and the other because of flare at 6 months. Our findings suggest that TCZ monotherapy may be an alternative treatment option for MPA patients who are intolerant to GC.

Eosinophilic granulomatosis with polyangiitis is an eosinophilic vasculitis and has different pathophysiological features to GPA and MPA. Although systemic GCs are the cornerstone of the treatment for EGPA, most patients remain dependent on GC therapy and relapses are common [41]. There is therefore a need for additional, more effective therapies. The cytokine interleukin (IL)-5 regulates eosinophil proliferation, maturation and differentiation and is present at increased levels in patients with EGPA [42]. Mepolizumab, an anti-IL-5 monoclonal antibody, was reported to be effective for EGPA in a multicenter, double-blind, parallel-group and phase 3 trial [43]. A total of 136 participants underwent randomization, with 68 assigned to receive mepolizumab and 68 to receive placebo. Mepolizumab treatment led to significantly more accrued weeks of remission than placebo (28% vs. 3% of participants had ≥24 weeks of accrued remission; \( p < .001 \)) and a higher percentage of patients in remission at both week 36 and 48 (32% vs. 3%; \( p < .001 \)). In addition, mepolizumab group patients required a lower average dose of PSL than the placebo group. Mepolizumab may therefore have both clinical and steroid-sparing effects in the treatment of EGPA.

5. Adult-onset Still’s disease

Adult-onset Still’s disease (AOSD) is a rare inflammatory disorder characterized by the classic triad of daily spiking fevers, arthritis and a unique salmon-colored rash. The pathophysiology of AOSD remains obscure, and identification of an etiological trigger is still lacking [44]. Nevertheless, strong correlations have been observed between inflammatory cytokines, such as IL-6, IL-1 and IL-18, and AOSD. AOSD patients usually require moderate to large amounts of GCs (PSL 0.6–1.0 mg/kg) [44]. Although GCs are effective in most patients, some cases do not go into remission or they relapse after the GC dose is tapered; other cases develop GC-related side effects such as osteoporotic vertebral fractures. Recent studies have reported the effectiveness of biological agents in the treatment of AOSD. While IL-1 therapy has demonstrated efficacy in refractory disease [45], novel therapies targeting IL-6 and IL-18 show great promise and are currently under investigation [44,46].

Anakinra, an IL-1 receptor antagonist, has demonstrated efficacy and GC-sparing effects in case reports and case series of AOSD [45,47]. TCZ successfully led to remission and enabled tapering or discontinuation of concomitant GCs in 13 refractory AOSD patients, and two AOSD patients were
These biological agents enable the reduction or elimination of GCs and may constitute an alternative treatment strategy for GC-intolerant AOSD patients.

6. Conclusions

While GCs remain the mainstay of treatment options for many IMIDs, the development of new therapeutic strategies combined with cytotoxic agents and new drugs such as biological agents has changed the need for GC. In particular, biological agents have caused a paradigm shift in the treatment of RA and have prompted the need for increased understanding of the differences in the pathophysiological mechanisms of various inflammatory diseases. In addition, targeted low molecular weight compounds, such as cytokine signaling inhibitors (such as Janus kinase [JAK] and Bruton’s tyrosine kinase [BTK] inhibitors), are expected to be as effective as biological agents against IMIDs. While there is no doubt that large-scale randomized placebo-controlled studies are effective, these are difficult to conduct for rare diseases, making case reports and case series equally important for drugs aimed at such diseases. Future treatment strategies that enable the use of lower doses of GCs or eliminate their need above the minimum use are needed. Current drug development studies indicate that the era of GC-sparing or GC-free treatment for IMIDs is on the horizon.

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References

[1] van der Goes MC, Jacobs JW, Bijlsma JW. The value of glucocorticoid co-therapy in different rheumatic diseases – positive and adverse effects. Arthritis Res Ther. 2014;16(Suppl 2):S2.

[2] Chen S-Y, Choi C-B, Li Q, et al. Glucocorticoid use in patients with systemic lupus erythematosus: association between dose and health care utilization and costs. Arthritis Care Res (Hoboken). 2015;67:1086–1094.

[3] Kuck A, Hazleman BL, Ostor AJK, et al. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J. 2007;83:251–260.

[4] Kopf M, Bachmann MF, Marsland BJ, et al. Averting inflammation by targeting the cytokine environment. Nat Rev Drug Discov. 2010;9:703–718.

[5] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365:2205–2219.

[6] Smolen JS, Aletaha D, McInnes IB, et al. Rheumatoid arthritis. Lancet. 2016;388:2023–2038.

[7] Davidson A, Diamond B. Autoimmune diseases. N Engl J Med. 2001;345:340–350.

[8] Singh JA, Saag KG, Bridges SL, et al. 2015 American college of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. (Hoboken). 2016;68:1–26.

[9] Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76:960–977.

[10] van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76:978–991.

[11] Takeuchi T, Pitrowski P, Lianeri M, et al. CD3 z defects in systemic lupus erythematosus. Ann Rheum Dis. 2012;71(Suppl 2):78–81.

[12] Hahn BH, McMahon MA, Alan W, et al. American college of rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64:797–808.

[13] Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71:1771–1782.

[14] Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005;353:2219–2228.

[15] Li X, Ren H, Zhang Q, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrol Dial Transplant. 2012;27:1467–1472.

[16] Borchers AT, Leibshor N, Naguwa SM, et al. Lupus nephritis: a critical review. Autoimmun Rev. 2012;11:174–194.

[17] Furie R, Nicholls K, Cheng T-T, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheumatol. 2014;66:379–389.

[18] van Vollenhoven RF, Parodis I, Levitsky A, et al. Biologics in SLE: towards new approaches. Best Pract Res Clin Rheumatol. 2013;27:341–349.

[19] Bao H, Liu Z-H, Xie H-L, et al. Successful treatment of class V + IV lupus nephritis with multitarget therapy. J Am Soc Nephrol. 2008;19:2001–2010.
Kurasawa T, Nagasawa H, Nishi E, et al. Successful treatment of class IV + V lupus nephritis with combination therapy of high-dose corticosteroids, tacrolimus and intravenous cyclophosphamide. Intern Med. 2013;52:1125–1130.

[21] Sakai R, Kurasawa T, Nishi E, et al. Efficacy and safety of multitarget therapy with cyclophosphamide and tacrolimus for lupus nephritis: a prospective, single-arm, single-centre, open label pilot study in Japan. Lupus. 2018;27:273–282.

[22] Condon MB, Ashby D, Pepper RJ, et al. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis. 2013;72:1280–1286.

[23] Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1–11.

[24] Buttigereit F, Dejaco C, Matteson EL, et al. Polymyalgia rheumatica and giant cell arteritis: a systematic review. JAMA. 2016;315:2442–2458.

[25] Gabriel SE, Sunku J, Salvarani C, et al. Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica. Arthritis Rheum. 1997;40:1873–1878.

[26] Wilson JC, Sarsour K, Collinson N, et al. Serious adverse effects associated with glucocorticoid therapy in patients with giant cell arteritis (GCA): a nested case-control analysis. Semin Arthritis Rheum. 2017;46:819–827.

[27] Kermani TA, Dasgupta B. Current and emerging therapies in large-vessel vasculitis. Rheumatology (Oxford). 2017. Epub ahead of print.

[28] Villiger PM, Adler S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2016;387:1921–1927.

[29] Stone JH, Tuckwell K, Sophie D, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med. 2017;377:317–328.

[30] Nakaoka Y, Isobe M, Takei S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomized, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis. 2018;77:348–354.

[31] Devauchelle-Pensec V, Berthelot JM, Cornec D, et al. Efficacy of first-line tocilizumab therapy in early polymyalgia rheumatica: a prospective longitudinal study. Ann Rheum Dis. 2016;75:1506–1510.

[32] Lally L, Forbess L, Hatzis C, et al. Brief report: a prospective open-label phase IIa trial of tocilizumab in the treatment of polymyalgia rheumatica. Arthritis Rheumatol. 2016;68:2550–2554.

[33] Dejaco C, Brouwer E, Mason JC, et al. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol. 2017;13:578–592.

[34] Kallenberg CG. Key advances in the clinical approach to ANCA-associated vasculitis. Nat Rev Rheumatol. 2014;10:484–493.

[35] Little MA, Nightingale P, Verburgh CA, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis. 2010;69:1036–1043.

[36] Stone JH, Merkel PA, Robert S, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221–232.

[37] Guillemin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371:1771–1780.

[38] Berti A, Cavalli G, Campochiaro C, et al. Interleukin-6 in ANCA-associated vasculitides: rationale for successful treatment with tocilizumab. Semin Arthritis Rheum. 2015;45:48–54.

[39] Sakai R, Kondo T, Kurasawa T, et al. Current Clinical evidence of tocilizumab for the treatment of ANCA-associated vasculitis: a prospective case series with corticosteroids and literature review. Clin Rheumatol. 2017;36:2382–2392.

[40] Sakai R, Kondo T, Kikuchi J, et al. Corticosteroid-free treatment of tocilizumab monotherapy for microscopic polyangiitis: a single-arm, single-center, clinical trial. Mod Rheumatol. 2016;26:900–907.

[41] Comarmond C, Pagnoux C, Khellaf M, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum. 2013;65:270–281.

[42] Hellmich B, Csernok E, Gross WL, et al. Proinflammatory cytokines and autoimmunity in Churg-Strauss syndrome. Ann NY Acad Sci. 2005;1051:121–131.

[43] Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med. 2017;376:1921–1932.

[44] Siddiqui M, Putman MS, Dua AB, et al. Adult-onset Still’s disease: current challenges and future prospects. Open Access Rheumatol. 2016;8:17–22.

[45] Nordström D, Knight A, Luukkainen R, et al. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still’s disease. An open, randomized, multicenter study. J Rheumatol. 2012;39:2008–2011.

[46] Sakai R, Nagasawa H, Nishi E, et al. Successful treatment of adult-onset Still’s disease with tocilizumab monotherapy: two case reports and literature review. Clin Rheumatol. 2012;31:569–574.

[47] Ortiz-Sanjúan F, Blanco R, Riancho-Zarrabezita L, et al. Efficacy of anakinra in refractory adult-onset Still’s Disease: multicenter study of 41 patients and literature review. Medicine (Baltimore). 2015;94:e1554.