REVIEW

Biologic Therapy for the Treatment of Giant Cell Arteritis

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ABSTRACT

Giant cell arteritis (GCA), a vasculitis of the medium and large arteries, is traditionally managed with glucocorticoids. However, the side effects of chronic glucocorticoid use and the occurrence of refractory cases warrant the consideration of steroid-sparing agents, including biologic agents. Interleukin-6 (IL-6) inhibition shows the most promise as biologic therapy for refractory cases of GCA, but data to support the use of other existing biologic agents are currently lacking. A better understanding of the pathogenesis of GCA as well as clinical trials investigating both existing and emerging biologic agents is needed to expand therapeutic options for the treatment of GCA.

Keywords: Biologics, giant cell arteritis, temporal arteritis, TNF α inhibitors, tocilizumab

INTRODUCTION

Giant cell arteritis (GCA) is a vasculitis of medium- and large-sized arteries. The vascular bed of the cranial arteries is most commonly involved, but it can also affect the aorta and its primary and secondary branches. The standard therapy remains glucocorticoids, with some patients requiring prolonged therapy for 1 to 2 years.¹ Although prednisone leads to a rapid response in the majority of patients, it is associated with a number of adverse events ranging from diabetes mellitus, hypertension, and cataracts to osteoporosis and infection. As many as 86% of patients with GCA experience side effects of glucocorticoids.¹ The prevalence of adverse events due to glucocorticoids has led to research efforts looking for alternative treatments for GCA.

To date, methotrexate has been examined the most extensively as an alternative treatment to glucocorticoids, but data regarding its effectiveness have been inconclusive. Two studies by Van der Veen et al. in 1996 and Spiera et al. in 2001 demonstrated no steroid-sparing effect with methotrexate.^{2,3} These findings are in contrast to work by Jover et al.

in 2001 and Caporali et al. in 2004 showing methotrexate to be an effective alternative.^{4,5} Current research examines biologic therapy that targets specific cytokines as treatment options for GCA based on the pathophysiology of the disease.

GCA is characterised by the presence of a mononuclear cellular infiltration affecting all the layers of the wall of the involved artery. The initial period of inflammation involves T cell infiltration of the vessel wall via Toll-like receptors in the adventitia, leading to activation of the immune system and subsequent chemokine production. This phase is followed by the recruitment of monocytes, additional T cells, and the eventual formation of granulomas and multinucleated giant cells. The resultant chemokine production leads to fragmentation of the elastic lamina, loss of smooth muscle, intimal hyperplasia, and eventual artery occlusion.^{6,7} Further examination of the pro-inflammatory cytokines has demonstrated an increase in interleukin-1 (IL-1), tumour necrosis factor (TNF) α , and IL-6, with IL-6 most closely correlating with disease expression and severity.^{8,9} The targeting of these cytokines may represent potential treatment options for giant cell arteritis.

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BIOLOGIC THERAPY

Tissue Necrosis Factor α Inhibitors

Tissue necrosis factor α (TNF α), a pro-inflammatory cytokine that has been targeted successfully in inflammatory arthritides such as rheumatoid arthritis and seronegative spondyloarthropathies, may play a role in the pathogenesis of GCA. Elevated TNF α concentrations in both tissue and serum are associated with active GCA.¹⁰ However, there is little evidence to date that supports its standard use as a steroid-sparing agent in GCA. Currently, TNF α inhibitors approved for use by the National Institute for Health and Care Excellence (NICE) in the United Kingdom and the United States Food and Drug Administration (FDA) include three anti-TNF α immunoglobulin G1 (IgG1) antibodies (infliximab, adalimumab, golimumab), one pegylated antibody fragment (certolizumab), and a Fc-fusion protein (etanercept).^{11–18}

Infliximab, the TNF α inhibitor most studied in GCA, is a chimeric murine-human monoclonal antibody that binds to TNF α , blocking its interaction with the TNF α receptor. Infliximab is administered as an intravenous infusion of 5 mg/kg at 0, 2, and 6 weeks, followed by every 8 weeks. Doses range from 3 to 10 mg/kg and are given in combination with weekly methotrexate to minimise the formation of human anti-chimeric antibodies and thereby increase infliximab serum concentrations.¹⁹

The first open study reporting successful use of infliximab described excellent responses in three of four patients with active GCA who had not tolerated tapering of prednisone doses lower than 7.5–12.5 mg/day. Remission was achieved for up to 5 months.²⁰ Additional case reports have suggested that TNF α inhibition may play a therapeutic role in GCA.^{21–23} However, a randomised controlled trial comparing infliximab with placebo in 44 newly diagnosed GCA patients on a tapering dose of glucocorticoids showed contrasting results. Infliximab therapy, compared with placebo, did not increase the proportion of patients who were relapse-free at week 22 (0.43 versus 0.50; $p=0.65$). Use of infliximab also did not decrease the cumulative dose of glucocorticoids required, or the mean dose at relapse. Moreover, infections were observed in 71% of patients in the infliximab group versus 56% in the placebo group, although the difference was not statistically significant. The study was terminated early at week 22 due to the observed lack of efficacy of infliximab. Investigators concluded that the use of infliximab is of no benefit in the treatment of patients with glucocorticoid-induced remission of newly diagnosed GCA and may be harmful.²⁴

Other commonly utilised TNF α inhibitors, adalimumab and etanercept, have been reportedly successful in GCA, but only in single case reports.^{25,26} Adalimumab is a humanised IgG1 monoclonal antibody that binds TNF α and is administered

subcutaneously as a 40 mg dose once every 2 weeks. It is approved for use in ankylosing spondylitis, Crohn's disease, psoriasis, psoriatic arthritis, and rheumatoid arthritis by the NICE and the FDA.^{27–31} Adalimumab is also approved for use in ulcerative colitis by the FDA.³² A recent double-blind randomised controlled trial evaluated the addition of adalimumab versus placebo to standard treatment in 70 patients with newly diagnosed GCA. Using intention to treat analysis, the study did not demonstrate a difference between proportions of patients in the infliximab and placebo groups that reached remission on less than 0.1 mg/kg of prednisone at week 26 (58.9% versus 50.0%, $p=0.46$).³³

Etanercept, a soluble TNF-receptor fusion protein, which also binds TNF α , is administered subcutaneously as a weekly 50 mg dose. Worth noting are descriptions of the development of GCA in patients taking adalimumab³⁴ or etanercept³⁵ for rheumatoid arthritis. These findings warrant caution in the use of TNF α inhibitors for GCA, even in refractory cases.

Certolizumab pegol and golimumab, the newest biologic agents to be added to the armamentarium of TNF α inhibitors, are administered subcutaneously once a month. Certolizumab pegol is approved for the treatment of rheumatoid arthritis in the USA and in Europe. It is also approved for the treatment of Crohn's disease in the USA, but not in Europe.³⁶ Golimumab is approved for use in ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis in both the UK and the USA.^{37,38} Golimumab is also approved for the treatment of ulcerative colitis in the USA.³⁹ Neither certolizumab pegol nor golimumab have been studied in GCA, but their efficacy is expected to be similar to that of previously discussed TNF α inhibitors.

Interleukin-6 Inhibition

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that plays an important role in the pathophysiology of GCA. Studies have shown significantly elevated IL-6 concentrations in the serum of untreated GCA patients when compared with normal controls⁴⁰ and have also demonstrated IL-6 production by vascular infiltrates in GCA biopsy specimens.⁴¹ IL-6 is a potent inducer of acute-phase responses and is located upstream of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are inflammatory markers used to monitor GCA disease activity. Serum levels of IL-6 correlate closely with disease activity, as exhibited by a prompt decline in the IL-6 levels of patients with GCA on steroid therapy, and significant elevation in the setting of GCA relapse.⁴¹ Given that the role of IL-6 in GCA has been well established, IL-6 has become an attractive target for treatment of the disease.⁴²

Tocilizumab (TCZ) is a humanised monoclonal anti-IL-6 receptor antibody that binds both soluble

and membrane bound IL-6 receptors and works by inhibiting IL-6 signal transduction; it is administered as a monthly infusion of either 4 or 8 mg/kg. TCZ was initially FDA approved for the treatment of rheumatoid arthritis in 2010 and was later approved for systemic juvenile idiopathic arthritis in the USA as well.⁴³ Additionally, TCZ is approved by NICE for use in both rheumatoid arthritis and systemic juvenile idiopathic arthritis in the UK.^{44,45} Since that time there have been many reports of successful treatment of other inflammatory rheumatic diseases with TCZ.⁴⁶

The first case report of TCZ use in GCA patients was published in 2011, and since that time there have been numerous case reports and case series reporting the results of 20 patients with GCA that have been successfully treated with TCZ (Table 1).⁵⁵ The earliest report describes a 63-year-old female with biopsy-proven GCA complicating refractory polymyalgia rheumatica who had previously failed methotrexate, leflunomide, and azathioprine. She was unable to discontinue steroids until she was treated with TCZ, at which point she experienced prompt symptomatic and serological improvement, thus allowing steroid taper and sustained clinical remission.⁵⁵ Beyer et al. reported clinical and radiographic response in three refractory GCA patients who received 6 months of TCZ after failure of azathioprine, mycophenolate mofetil, and methotrexate to allow weaning of prednisone below 30 mg daily. Treatment with TCZ for 24 weeks allowed all three patients to wean steroids to 7.5 mg prednisone daily or less, and positron-emission tomography/computed tomography (PET/CT) scan, which had previously shown increased uptake in two of the cases, had normalised.⁴⁸ Seitz et al. reported a series of five GCA patients, two of whom had failed glucocorticoid with concomitant methotrexate therapy, one who was unable to wean off glucocorticoid therapy, and two of whom were treatment naïve.⁵⁵ All five of their patients were in complete remission at a mean follow up of 8.3 months, with three patients still

receiving TCZ infusions and two patients in remission off of all therapy. Thus, there is evidence that TCZ can be used in GCA as a steroid-sparing agent to allow glucocorticoid taper and a smaller amount of evidence that it may also be effective as monotherapy in treatment naïve patients.

There is one retrospective study evaluating TCZ therapy for treatment of large-vessel vasculitis. The study included 10 patients, seven having GCA (six biopsy-proven) and all having either treatment refractory or experiencing intolerable side effects from their treatment regimens. With the exception of two patients who received 4 mg/kg/month, most patients received 8 mg/kg/month dosing of TCZ. All patients were clinically and serologically improved after 8–12 weeks of TCZ, and prednisone was tapered to 6 mg daily or less; clinical remission was maintained for the duration of TCZ therapy and all other immunosuppressants were discontinued. Adverse outcomes noted in this study include leukopenia, neutropenia, and mild transaminitis. Interestingly, one patient died of unrelated causes while in clinical and serological remission for at least 4 months, although an autopsy showed active GCA involving multiple vessels.⁴⁴

Although TCZ therapy for GCA does seem promising based on the preliminary reports summarised above, the need remains for large-scale, prospective, randomised studies. Two such studies are in progress. The first is a Phase II, randomised placebo-controlled study currently being conducted to assess the ability of TCZ combined with glucocorticoids to induce remission in GCA patients at week 12 as compared with placebo combined with glucocorticoids. The estimated study completion date is March 2014.⁵⁷ Another study, the GiACTA Trial, has been designed as a multicentre, randomised, double-blind, and placebo-controlled study to evaluate the efficacy of TCZ in combination with a 6-month prednisone taper to sustain a 52-week remission. This trial will use subcutaneous TCZ at weekly or

TABLE 1. Summary of case reports of the use of tocilizumab for treatment of giant cell arteritis.

Authors	No. of patients	Previous therapy	Reason for TCZ	Initial dosing of TCZ	Outcome
Besada et al. ⁴⁷	1	GC, MTX	Refractory disease	8 mg/kg	Remission
Beyer et al. ⁴⁸	3	MTX, AZA	Inability to taper GC	8 mg/kg	Remission
Christidis et al. ⁴⁹	1	MTX, LEF, AZA	Refractory disease	8 mg/kg	Remission
Isik et al. ⁵⁰	1	GC, CYC, MMF	Refractory disease	8 mg/kg	Remission
Lurati et al. ⁵¹	1	GC	Inability to taper GC	8 mg/kg	Remission
Salvarani et al. ⁵²	2	GC (1); Treatment naïve (1)	Inability to taper GC (1); Patient reluctance to take GC (1)	8 mg/kg	Remission
Schafer et al. ⁵³	3	GC	Inability to taper GC	8 mg/kg	Remission
Sciascia et al. ⁵⁴	2	MTX	Inability to taper GC	8 mg/kg	Remission
Seitz et al. ⁵⁵	5	GC, MTX; Treatment naïve (2)	Inability to taper GC	8 mg/kg	Remission
Vinit et al. ⁵⁶	1	MTX, GC	Inability to taper GC	8 mg/kg	Remission

TCZ, tocilizumab; GC, glucocorticoid; MTX, methotrexate; AZA, azathioprine; LEF, leflunomide; CYC, cyclophosphamide; MMF, mycophenolate mofetil.

biweekly intervals and will compare these regimens with two different prednisone monotherapy regimens. The protocol will consist of a 52-week blinded treatment phase followed by an open-label extension of 104 weeks.⁵⁸

Important questions remain regarding the optimal dosing, duration of therapy, adverse events, and how best to monitor for relapse in patients who are receiving TCZ. Both 8 mg/kg/month and 4 mg/kg/month have been shown to be effective in the cases described above and duration of therapy has varied. Some patients have relapsed after discontinuation of TCZ, suggesting that long-term therapy may be needed in select populations. Finally, blockade of the IL-6 receptor will, by default, lower or normalise the inflammatory markers that we typically use to monitor disease status in GCA patients. If TCZ does become a mainstream therapy for GCA, additional research into other biomarkers or methods of monitoring for relapse will need to be investigated.⁵⁹ This issue is especially important considering the patient described by Unizony *et al.* who was in apparent clinical and serological remission, but was found to have active vasculitis on autopsy.⁴²

In conclusion, there are promising preliminary reports of TCZ being effective for treatment of GCA as both monotherapy and as a steroid-sparing agent. Large-scale studies are underway to help better answer some of the questions regarding effectiveness, optimal dosing and duration, monitoring, and adverse events.

IL-1 Inhibitors

Presently, there are three medications available for IL-1 pathway inhibition: anakinra, an IL-1 receptor antagonist; riloncept which is an IL-1 receptor fusion protein; and canakinumab, a human IL-1 β antibody. These agents are used in the treatment of a variety of diseases including rheumatoid arthritis, systemic onset juvenile inflammatory arthritis, and neonatal-onset multisystem inflammatory disease. Data regarding their use for the treatment of GCA are scarce.

A number of animal models exist in demonstrating the role of IL-1 in the development of arteritis. Shepard and Nicklin describe the development of arteritis in IL-1 receptor antagonist-deficient mice.⁶⁰ However, literature regarding the use of IL-1 inhibition for GCA is limited to case reports, with no prospective or randomised studies to date. Ly and colleagues report three cases of refractory GCA treated successfully with IL-1 inhibition.⁶¹ These patients had improvement in inflammatory markers and/or symptoms, with two patients having resolution of arterial inflammation detected by PET/CT scans. Randomised controlled studies will need to be completed before the use of IL-1 inhibitors can be supported for the treatment of GCA.

Other Biologic Therapies

Rituximab, a monoclonal anti-CD20 antibody that targets B cells, has only been reported as a successful adjunctive agent in one case of refractory GCA.⁶² There are no reports or studies involving the use of other biologic agents such as abatacept, an inhibitor of T cell co-stimulation, in GCA.

CONCLUSION

Giant cell arteritis, a vasculitis characterised by inflammation of the medium and large arteries, is currently managed with a prolonged course of glucocorticoids, and in some cases, steroid-sparing agents such as oral methotrexate. However, the adverse side effects of chronic glucocorticoid use and the occurrence of refractory cases warrant the consideration of effective steroid-sparing agents such as biologic therapy. TCZ, an anti-IL6 antibody, shows the most promise as a treatment for refractory cases of GCA or individuals who cannot tolerate prolonged courses of glucocorticoids. TNF α inhibition, though effective in other rheumatologic conditions, is not recommended for use in GCA. Use of IL-1 inhibition also lacks data to support its use in GCA. A better understanding of immunologic key players in the pathogenesis of GCA is needed to develop specific and effective steroid-sparing therapy, and clinical trials are needed to determine the utility of existing biologic therapy for the treatment of GCA.

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REFERENCES

- [1] Proven A, Gabriel SE, Orces C, O'Fallon M, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003;49:703–708.
- [2] Van der Veen MJ, Dinant HJ, Van Booma-Frankfort C, Van Albada-Kuipers GA, Bijlsma JW. Can methotrexate be used as a steroid sparing agent in the treatment of polymyalgia rheumatic and giant cell arteritis? *Ann Rheum Dis* 1996;55:218–223.
- [3] Spiera RF, Mitnick HJ, Kupersmith M, Richmond M, Spiera H, Peterson MG, Paget SA. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheum* 2001;19:495–501.
- [4] Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;134:106–114.
- [5] Caporali R, Cimmino MA, Ferraccioli G, Gerli R, Klersy C, Salvarani C, Moneta C. Prednisone plus methotrexate for polymyalgia rheumatic: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2004;141:493–500.

- [6] Weyand CM. The Dunlop-Dottridge Lecture: the pathogenesis of giant cell arteritis. *J Rheumatol* 2000;27:517–522.
- [7] Weyand CM, Wagner AD, Björnsson J, Goronzy JJ. Correlation of the topographical arrangement and the functional pattern of tissue-infiltrating macrophages in giant cell arteritis. *J Clin Invest* 1996;98:1642–1649.
- [8] Hernández-Rodríguez J, Segarra M, Vilardell C, Sánchez M, García-Martínez A, Esteban MJ, Queralto C, Grau JM, Urbano-Márquez A, Palacín A, Colomer D, Cid MC. Tissue production of pro-inflammatory cytokines (IL-1B, TNF alpha and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. *Rheumatology* 2004;43:294–301.
- [9] Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatic and giant cell arteritis. *Arthritis Rheum* 1993;36:1286–1294.
- [10] Visvanathan S, Rahman MU, Hoffman GS, Xu S, Garcia-Martinez A, Segarra M, Lozano E, Espigol-Frigole G, Hernandez-Rodriguez J, Cid MC. Tissue and serum markers of inflammation during the follow-up of patients with giant-cell arteritis—a prospective longitudinal study. *Rheumatology* 2011;50:2061–2070.
- [11] National Institute for Health and Care Excellence. (2007 Oct 24). TA130 Rheumatoid arthritis—adalimumab, etanercept and infliximab: guidance. Retrieved from <http://guidance.nice.org.uk/TA130/Guidance/pdf/English>.
- [12] US Food and Drug Administration. (1999 Nov 10). Infliximab Product Approval Info—Licensing Action. Retrieved from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm093335.htm>.
- [13] US Food and Drug Administration. (2002 Dec 31). Adalimumab Product Approval—Licensing Action. Retrieved from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080610.htm>.
- [14] National Institute for Care and Health Excellence (2011 Jun 22). TA225. Rheumatoid arthritis (after the failure of previous anti-rheumatic drugs)—golimumab: guidance. Retrieved from <http://www.nice.org.uk/guidance/TA225/Guidance/pdf>
- [15] U.S Food and Drug Administration. (2009 Apr 24). Drug Approval Package: Simponi (Golimumab) Injection. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125289s0000TOC.cfm
- [16] National Institute for Care and Health Excellence. (2010 Feb 24). TA186. Rheumatoid arthritis—certolizumab pegol: guidance. Retrieved from <http://guidance.nice.org.uk/TA186/Guidance/pdf/English>
- [17] US Food and Drug Administration. (2008 Apr 28). Drug Approval Package: Cimzia (Certolizumab Pegol) Injection. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/125160s000TOC2.cfm.
- [18] US Food and Drug Administration. (1998 Dec 2). Etanercept Product Approval Information. Retrieved from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080536.htm>
- [19] Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, Antoni C, Leeb B, Elliott MJ, Woody JN, Schaible TF, Feldmann M. Therapeutic efficacy of multiple intravenous infusions of anti-tumour necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; 41:1552–1563.
- [20] Cantini F, Niccoli L, Salvarani C, Padula A, Olivieri I. Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum* 2001;44: 2933–2935.
- [21] Torrente SV, Guerri RC, Perez-Garcia C, Benito P, Carbonell J. Amaurosis in patients with giant cell arteritis: treatment with anti-tumour necrosis factor-alpha. *Intern Med* 2007;37:280–281.
- [22] Uthman I, Kanj N, Atweh S. Infliximab as monotherapy in giant cell arteritis. *Clin Rheumatol* 2006;25:109–110.
- [23] Airo P, Antonioli CM, Vianelli M, Toniati P. Antitumour necrosis factor treatment with infliximab in a case of giant cell arteritis resistant to steroid and immunosuppressive drugs. *Rheumatology* 2002;41:347–349.
- [24] Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, Salvarani C, Xu W, Visvanathan S, Rahman MU; Infliximab-GCA Study Group. Infliximab for maintenance of glucocorticosteroid-induced remission of giant-cell arteritis. *Ann Intern Med* 2007;146:621–630.
- [25] Ahmed MM, Mubashir E, Hayat S, Fowler M, Berney SM. Treatment of refractory temporal arteritis with adalimumab. *Clin Rheumatol* 2007;26:1353–1355.
- [26] Tan AL, Holdsworth J, Pease C, Emery P, McGonagle D. Successful treatment of resistant giant cell arteritis with etanercept. *Ann Rheum Dis* 2003;62:373–374.
- [27] National Institute of Health and Care Excellence. (2008 May 28). TA143. Ankylosing spondylitis—adalimumab, etanercept and infliximab: guidance. Retrieved from <http://guidance.nice.org.uk/TA143/Guidance/pdf/English>.
- [28] National Institute of Health and Care Excellence. (2010 May 29). TA187. Crohn's disease—infliximab (review) and adalimumab (review of TA40): guidance. Retrieved from <http://guidance.nice.org.uk/TA187/Guidance/pdf/English>.
- [29] National Institute of Health and Care Excellence. (2008 Jun 25). TA146. Psoriasis—adalimumab: NICE guidance. Retrieved from <http://guidance.nice.org.uk/TA146/Guidance/pdf/English>.
- [30] National Institute of Health and Care Excellence. (2010 Aug 25). TA199. Psoriatic arthritis—etanercept, infliximab and adalimumab: guidance. Retrieved from <http://guidance.nice.org.uk/TA199/Guidance/pdf/English>.
- [31] US Food and Drug Administration. (2011 Dec). Humira (adalimumab) label. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125057s0276lbl.pdf.
- [32] US Food and Drug Administration. (2012 Sep 28). FDA approves Humira to treat ulcerative colitis. Retrieved from <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm321650.htm>.
- [33] Seror R, Baron G, Hachulla E, Debandt M, Larroche C, Puéchal X, Maurier F, de Wazieres B, Quémeuneur T, Ravaud P, Mariette X. Clinical and epidemiological research: extended report: adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. *Ann Rheum Dis* Epub ahead of print 29 July 2013. doi: 10.1136/annrheumdis-2013-203586.
- [34] Leydet-Quilici H, Luc M, Armingeat T, Pham T, Lafforgue P. Giant cell arteritis during adalimumab treatment for rheumatoid arthritis. *Joint Bone Spine* 2007;74:303–304.
- [35] Seton M. Giant cell arteritis in a patient taking etanercept and methotrexate. *J Rheumatol* 2004;31:1467.
- [36] US Food and Drug Administration. (2008 Apr 28). FDA approves cimzia to treat Crohn's disease. Retrieved from

- <http://www.fda.gov/newsevents/newsroom/pressannouncements/2008/ucm116882.htm>.
- [37] National Institute of Health and Care Excellence. (2011 Aug 24). TA233. Ankylosing spondylitis—golimumab: guidance. Retrieved from <http://guidance.nice.org.uk/TA233/Guidance/pdf/English>.
 - [38] National Institute of Health and Care Excellence. (2011 Apr 27). TA220. Psoriatic arthritis—golimumab: guidance. Retrieved from <http://guidance.nice.org.uk/TA220/Guidance/pdf/English>.
 - [39] US Food and Drug Administration. (2013 Nov). Full Prescribing Information: Golimumab. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125289s0941bl.pdf.
 - [40] Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. *Arthritis Rheum* 1993;36:1286–1294.
 - [41] Weyand CM, Fulbright JW, Hunder GG, Evans JM, Goronzy JJ. Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. *Arthritis Rheum* 2000;43:1041–1048.
 - [42] Unizony S, Arias-Urdaneta L, Miloslavsky E, Arvikar S, Khosroshahi A, Keroack B, Stone JR, Stone JH. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, takayasu arteritis) and polymyalgia rheumatica. *Arthritis Care Res* 2012;64:1720–1729.
 - [43] Alten R, Maleitzke T. Tocilizumab: a novel humanized anti-interleukin 6 (IL-6) receptor antibody for the treatment of patients with non-RA systemic, inflammatory rheumatic diseases. *Ann Med* 2013;45:357–363.
 - [44] National Institute for Health and Care Excellence. (2011 Dec 14). TA238. Arthritis (juvenile idiopathic, systemic)—tocilizumab: guidance. Retrieved from <http://guidance.nice.org.uk/TA238/Guidance/pdf/English>.
 - [45] National Institute for Health and Care Excellence. (2012 Feb 22). TA247. Rheumatoid arthritis—tocilizumab (rapid review TA198): guidance. Retrieved from <http://guidance.nice.org.uk/TA247/Guidance/pdf/English>.
 - [46] Sakai R, Nagasawa H, Nishi E, Okuyama A, Takei H, Kurasawa T, Kondo T, Nishimura K, Shirai Y, Ito T, Kameda H, Takeuchi T, Amano K. Successful treatment of adult-onset Still's disease with tocilizumab monotherapy: two case reports and literature review. *Clin Rheumatol* 2012; 31:569–574.
 - [47] Besada E, Nossent JC. Ultrasonographic resolution of the vessel wall oedema with modest clinical improvement in a large-vessel vasculitis patient treated with tocilizumab. *Clin Rheumatol* 2012;31:1263–1265.
 - [48] Beyer C, Axmann R, Sahinbegovic E, Distler JH, Manger B, Schett G, Zwerina J. Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis. *Ann Rheum Dis* 2011;70:1874–1875.
 - [49] Christidis D, Jain S, Das Gupta B. Successful use of tocilizumab in polymyalgic onset biopsy positive GCA with large vessel involvement. *BMJ Case Rep Epub ahead of print* 2011 Jun 30. doi: 10.1136/bcr.04.2011.4135.
 - [50] Isik M, Kilic L, Dogan I, Calguneri M. Tocilizumab for giant cell arteritis: an amazing result. *Rheumatol Int* 2013;33:2961–2962.
 - [51] Lurati A, Bertani L, Re KA, Marrazza M, Bompane D, Scarpellini M. Successful treatment of a patient with giant cell vasculitis (horton arteritis) with tocilizumab a humanized anti-interleukin-6 receptor antibody. *Case Rep Rheumatol* 2012;2012:639612.
 - [52] Salvarani C, Magnani L, Catanoso M, Pipitone N, Versari A, Dardani L, Pulsatelli L, Meliconi R, Boiardi L. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. *Rheumatology* 2012;51:151–156.
 - [53] Schafer VS, Zwerina J. Biologic treatment of large-vessel vasculitides. *Curr Opin Rheumatol* 2012;24:31–37.
 - [54] Sciascia S, Rossi D, Roccatello D. Interleukin 6 blockade as steroid-sparing treatment for 2 patients with giant cell arteritis. *J Rheumatol* 2011;38:2080–2081.
 - [55] Seitz M, Reichenbach S, Bonel HM, Adler S, Wermelinger F, Villiger PM. Rapid induction of remission in large vessel vasculitis by IL-6 blockade. *A case series. Swiss Med Wkly* 2011;141:w13156.
 - [56] Vinit J, Bielefeld P, Muller G, Besancenot JF. Efficacy of tocilizumab in refractory giant cell arteritis. *Joint Bone Spine* 2012;79:317–318.
 - [57] Villiger PM, Seitz M. (2013 Oct). Tocilizumab for Patients with Giant Cell Arteritis. *ClinicalTrials.gov*. Retrieved from <http://clinicaltrials.gov/show/NCT01450137>.
 - [58] Unizony SH, Dasgupta B, Fischeleva E, Rowell L, Schett G, Spiera R, Zwerina J, Harari O, Stone JH. Design of the tocilizumab in giant cell arteritis trial. *Int J Rheumatol* 2013; 2013:912562.
 - [59] Unizony S, Stone JH, Stone JR. New treatment strategies in large-vessel vasculitis. *Curr Opin Rheumatol* 2013;25:3–9.
 - [60] Shepard J, Nicklin M. Elastic-vessel arteritis in interleukin-1 receptor antagonist-deficient mice involves effector Th1 cells and requires interleukin-1 receptor. *Circulation* 2005; 111:3135–3140.
 - [61] Ly K-H, Stirnemann J, Liozon E, Michel M, Fain O, Fauchais AL. Interleukin-1 blockade in refractory giant cell arteritis. *Joint Bone Spine* 2013. doi: 10.1016/j.jbspin.2013.06.004.
 - [62] Bhatia A, Ell PJ, Edwards JCW. Anti-CD20 monoclonal antibody (rituximab) as an adjunct in the treatment of giant cell arteritis. *Ann Rheum Dis* 2005;64:1099–1100.