Published in final edited form as:
Biol Blood Marrow Transplant. 2011 December ; 17(12): 1862–1868. doi:10.1016/j.bbmt.2011.07.001.

Tocilizumab for the Treatment of Steroid Refractory Graft-versus-Host Disease

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Abstract

Corticosteroid refractory graft-versus-host disease (GVHD) is one of the major challenges in the management of allogeneic stem cell transplant recipients. Although numerous agents have been employed to treat this patient population, no standardized second-line therapy exists. In this study, we report our experience with the administration of tocilizumab, an anti-interleukin 6 receptor antibody, in the treatment of steroid refractory GVHD. Tocilizumab was administered to 8 patients with refractory acute (n = 6) or chronic GVHD (cGVHD) (n = 2) once every 3 to 4 weeks. The majority of patients with acute GVHD (aGVHD) had grade IV organ involvement of the skin or gastrointestinal tract, whereas both patients with cGVHD had long-standing severe skin sclerosis at the time of treatment. There were no allergic or infusion-related adverse events. Treatment was discontinued in one patient over concerns that tocilizumab may have worsened preexisting hyperbilirubinemia. Several patients also had transient elevations in serum transaminase values. Infections were the primary adverse events associated with tocilizumab administration. Four patients (67%) with aGVHD had either partial or complete responses apparent within the first 56 days of therapy. One patient with cGVHD had a significant response to therapy, whereas the second had stabilization of disease that allowed for a modest reduction in immune suppressive medications. These results indicate that tocilizumab has activity in the treatment of steroid refractory GVHD and warrants further investigation as a therapeutic option for this disorder.

Keywords

Graft-versus-host disease; Interleukin 6; Tocilizumab; Steroid refractory

INTRODUCTION

Graft-versus-host disease (GVHD) is the major complication associated with allogeneic hematopoietic stem cell transplantation. For several decades, the initial management of acute GVHD (aGVHD) has been the administration of corticosteroids, and approximately 50% of patients will respond to this therapeutic intervention [1,2]. For those patients who fail to respond to steroids, a number of agents have been evaluated as second-line therapy, but no consensus has emerged for the treatment of these patients. Various modalities have been

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Financial disclosure: The authors have nothing to disclose.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2011.07.001.

employed to treat steroid refractory GVHD. These agents have generally fallen into broad categories, including cytostatic agents (mycophenolic acid, pentostatin) [3–5], immunomodulating agents (mTor inhibitors, thalidomide, photopheresis) [6–9], and biologic therapies (rituximab, alemtuzumab, infliximab, denileukin difitox) [10–14]. In this second-line treatment setting, response rates have generally been much lower (ie, on the order of 20%–30%), indicating the need for more effective therapies in this patient population.

A prominent characteristic of GVHD is the presence of a proinflammatory milieu that is attributable to conditioning regimen-induced host tissue damage as well as secretion of inflammatory cytokines by alloactivated donor T cells and other immune cell populations [15,16]. This has been the rationale for the administration of agents that interfere with inflammatory cytokine signaling for the therapy of GVHD. Interleukin 6 (IL-6) is a pleiotrophic cytokine that is produced by a variety of cell types and is reportedly elevated in the serum of patients with ongoing GVHD [17]. Moreover, polymorphisms in recipient and donor genotypes that result in increased IL-6 production have been associated with an increase in GVHD severity [18,19]. Recent studies in murine models of GVHD have shown that treatment with an anti-IL-6R antibody significantly reduces GVHD-associated mortality and pathological damage [20,21]. Whether this approach has merit for the treatment of patients with GVHD, however, has not been examined.

Tocilizumab (Actemra™, Roche, Indianapolis, IN) is a humanized anti-IL-6 receptor antibody that blocks IL-6 signaling and has been FDA approved for the treatment of severe active rheumatoid arthritis. It reportedly has remission-inducing efficacy in patients with moderate to severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, and multicentric Castlemans' disease [22–24]. A recent case report demonstrated that administration of tocilizumab was effective at significantly reducing the severity of GVHD in the gastrointestinal (GI) tract as determined by a marked reduction in the volume of diarrhea [25]. The purpose of this study was therefore to evaluate the efficacy and toxicity of tocilizumab in the treatment of a cohort of patients with steroid refractory GVHD.

PATIENTS, MATERIALS, AND METHODS

Patient Population

Eight patients were treated with off label use of tocilizumab at the discretion of their attending physicians from July 2010 to April 2011. Patients were deemed to be eligible for treatment if they had undergone allogeneic stem cell transplantation and developed steroid refractory, biopsy-proven GVHD, which could be in any tissue site (ie, skin, gut, etc.). Patients were classified as having steroid-resistant aGVHD if any of the following occurred: (1) no change or progression in the stage of skin GVHD after at least 1 week of 2 mg/kg per day or more of methylprednisolone in conjunction with extracorporeal photopheresis (ECP); (2) lack of response of visceral (liver, GI) GVHD despite treatment with 2 mg/kg per day or more of methylprednisolone for at least 72 hours; (3) progression of visceral GVHD despite treatment with 2 mg/kg per day or more of methylprednisolone for at least 48 hours; or (4) visceral GVHD progressing to stage 4 after 24 hours of 2 mg/kg per day or more of methylprednisolone. Patients with protracted acute GVHD who did not respond to a minimum of 0.5 mg/kg/day steroid therapy after 4 weeks were eligible. Finally, patients with classic chronic GVHD (cGVHD) who did not respond within 4 weeks after at least 0.5 mg/kg/day steroid therapy were also eligible. All patients provided written informed consent for hematopoietic progenitor cell transplantation under studies approved by the institutional review board (IRB) at the Medical College of Wisconsin (MCW). GVHD-related data were collected prospectively on each patient. The MCW IRB approved this retrospective analysis of tocilizumab therapy for steroid refractory GVHD.

Treatment

Tocilizumab was administered intravenously at a dose of 8 mg/kg once weekly every 3 to 4 weeks. Patients with documented responses continued to receive treatment on this schedule. Patients who had attained a complete remission were dose reduced to 4 mg/kg as long as they remained on other immune suppressive medications. Tocilizumab was discontinued once patients were able to be taken off all other immune suppressive medications and were free of GVHD for at least 1 month. Patients who did not respond to tocilizumab or had progression of disease were discontinued from therapy.

GVHD and Toxicity Assessment

The extent of aGVHD in GVHD target organs was graded according to the criteria enumerated in Glucksberg et al. [26]. The diagnosis of cGVHD was determined using the National Institutes of Health consensus criteria [27]. Scoring of skin and mucosal abnormalities in patients with cGVHD was based on criteria detailed in the cGVHD response criteria working group report [28]. Toxicity was assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Infection Monitoring

Blood and tissue-directed cultures for bacterial and fungal pathogens (ie, urine, sputum, etc.) were obtained at the discretion of the treating physician when clinically indicated. All patients had weekly cytomegalovirus (CMV) Nucleic Acid Amplified Test (NAAT) testing in the blood as well as Epstein-Barr virus (EBV), human herpes virus 6 (HHV-6), and adenovirus testing by polymerase chain reaction (PCR) in the blood at least every 2 weeks.

Response Definitions

Complete response (CR) was defined as an International Bone Marrow Transplant Registry (IBMTR) score of 0 for the GVHD grading in all evaluable organs. For a response to be scored as CR at day 56 or later, the participant must have been in CR on that day and have had no additional therapy for an earlier progression, partial response (PR), or no response (NR). PR was defined as improvement in 1 or more organs involved with GVHD symptoms without progression in others. For a response to be scored as PR at day 56 or later, the participant must have been in PR on that day and have had no intervening additional therapy for an earlier progression, PR, or NR. Mixed response (MR) was defined as improvement in 1 or more organs with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ. Progression was defined as deterioration in at least 1 organ without any improvement in others. NR was defined as progression with new organ involvement or increased organ-specific symptoms sufficient to increase the organ stage by 1 or more after at least 7 days of study drug administration, or no response (no reduction in any GVHD organ staging) after study drug administration. Patients receiving new additional secondary therapy (including the need to reescalate the steroid dose to ≥2.5 mg/kg/day of prednisone [or a methylprednisolone equivalent of 2 mg/kg/day]) were also classified as nonresponders.

Statistical Analysis

This study is a descriptive case series of 8 consecutive patients treated with tocilizumab for steroid refractory GVHD. Descriptive statistics with a median and a range were used to summarize the number of infusions. GVHD outcomes were described on an individual patient level.

RESULTS

Patient and Disease Characteristics

The patient characteristics are shown in Table 1. For all patients, except 1, this was the initial allogeneic stem cell transplant. Patient UPN 2272, who was transplanted for chronic lymphocytic leukemia (CLL), had failed his first nonmyeloablative transplant with persistent disease and evidence of graft rejection, and was then treated with a second myeloablative transplant from the same unrelated donor. All patients failed therapy with multiple other agents in addition to steroids (Table 2). Organ involvement in patients with acute GVHD consisted of lower GI tract disease in 5 patients (grade II in 1 and grade IV in 4) and skin involvement in 1 patient (grade IV). Two patients had classic cGVHD that was characterized by diffuse sclerosis of the skin with joint contractures.

Toxicity and Adverse Events

A total of 31 infusions of tocilizumab were administered during the study period. The median number of infusions was 5 per patient (range: 1–6 infusions), and the median time of administration posttransplantation was 4 months (range: 1–33 months). There was no infusion or allergic-related events. Two patients developed grade 2 elevations in serum transaminases at some time during the course of tocilizumab infusions. Of 31 total infusions, 8 were associated with elevated transaminase levels that were either grade 1 or 2 in severity. One patient (UPN 2031) had a preexisting grade 1 increase in serum aspartate aminotransferase/alanine aminotransferase (ALT/AST) values, but these remained unchanged during all infusions. Tocilizumab was discontinued in 1 patient (UPN 2503) after receiving a single infusion of this agent because of worsening of preexisting grade 1 hyperbilirubinemia. No other patients required discontinuation of this agent because of toxicity.

Infection Assessment

Five patients developed infections during treatment with 13 total documented infections. Nine (69%) of these infectious episodes were of bacterial origin and, except for 1 attributable to *Clostridium difficile* colitis, were because of bloodstream infections. Two patients developed fungal bloodstream infections attributable to *Fusarium* sp and *Candida* sp. Two other patients had viral infections; 1 with CMV colitis, which occurred temporally with grade 4GVHDof the gut, and a second with hemorrhagic cystitis because of BK viruria. CMV viremia was preexisting in 3 patients (UPN 2090, 2272, and 2292) before tocilizumab administration, having developed this condition 1 to 4 weeks before antibody treatment. Two patients cleared viremia after starting tocilizumab (4 months and 2 months, respectively). The third patient died 9 days after initiation of treatment with detectable CMV viremia without evidence of CMV disease. No patient developed CMV viremia after initiation of tocilizumab. None of these patients had evidence of EBV, HHV-6, or adenovirus reactivation or disease while on therapy.

Response to Treatment with Tocilizumab

The median time from onset of GVHD to administration of tocilizumab was 36 days (range: 8–260 days). An overall response was observed in 4 patients (67%) with aGVHD (Table 3). Two of 6 patients died with grade 4 aGVHD of the lower gastrointestinal tract. One patient had no demonstrable response to tocilizumab, whereas the second died 9 days after the first dose of tocilizumab with active GVHD and was deemed to be nonevaluable. Two patients had a complete response at day 56, whereas 2 others had partial responses. The complete responses were characterized by complete resolution of diarrhea. In the responding group of

patients, immune suppressive medications were reduced in all patients to varying degrees (Table 3).

Two patients (UPN 2031 and 2200) who were treated with tocilizumab had classic cGVHD, which was manifested predominantly by sclerosis of the skin that was long-standing and refractory to multiple prior immune suppressive medications (Table 2). No validated scoring system has been identified for the assessment of patients with sclerotic skin changes during cGVHD [29]. For that reason, we employed serial measurements of joint mobility as a surrogate indicator for skin sclerosis and also incorporated elements of the NIH consensus criteria for other aspects of skin GVHD [29]. One patient had stabilization of disease while taking tocilizumab. He had no alteration in his joint range of motion when serially evaluated by a physical therapist and no improvement noted on a cGVHD assessment scale. The steroid dose, however, was modestly reduced (Table 3). The second patient (UPN 2200) had a significant response to tocilizumab. The most severely affected area of skin sclerosis and joint contractures were in the lower extremities for this patient. The clinical response in this patient was characterized by measureable improvements in the range of motion in multiple joints, primarily in hip extension, knee flexion and extension, and ankle dorsiflexion (Supplementary Table 1). Increased flexibility in his lower extremities allowed for improved gait, which resulted in a significant augmentation in ambulation distance. Furthermore, there was improvement in overall skin and mucosal scores as well as a substantial reduction in his overall level of immune suppression.

DISCUSSION

In this report, we examined the efficacy of tocilizumab, an IL-6 receptor antibody that blocks signaling of IL-6, in the treatment of patients with steroid refractory GVHD. We observed overall clinical responses in 5 of 8 patients treated with tocilizumab. The majority of patients with aGVHD had overall grade 4 disease, with the GI tract being the predominant target organ. The median time from onset of GVHD to administration of tocilizumab was 29 days in this group. Thus, most patients who had failed steroids had persistent, severe GVHD for several weeks before tocilizumab was added to the regimen. Tocilizumab also appeared to have some efficacy in the treatment of skin sclerosis because of cGVHD. Both patients treated with this agent had failed multiple prior modalities and had significant functional limitations because of concurrent joint contractures. One patient had stabilization of disease, which was associated with a modest reduction in his steroid dose, whereas the second patient had a more dramatic response with objective improvement in joint mobility, a reduction in the amount of skin involvement, and substantial decrease in immune suppressive medications.

The rationale for the administration of tocilizumab derived from preclinical studies that had demonstrated that blockade of IL-6 signaling attenuates the severity of GVHD [20,21]. Protection from GVHD was attributed to a recalibration of the effector and regulatory arms of the immune system. This was characterized by a reduction in proinflammatory T_H1 and T_H17 cells with a commensurate increase in the number of regulatory T cells [20]. In particular, these preclinical studies demonstrated a role for IL-6 in mediating pathologic damage within the colon microenvironment as increased levels of IL-6 were also detected within the colon microenvironment [29]. Furthermore, blockade of IL-6 signaling with an anti-IL-6R antibody resulted in more profound protection in the colon relative to other GVHD target organs, such as the liver and lung. Thus, the clinical responses we observed in the gut in tocilizumab treated patients, coupled with a prior report [25], support a role for IL-6 in the pathophysiology of GI GVHD. Whether blockade of IL-6 signaling in allogeneic transplant recipients is able to augment reconstitution of regulatory T cells, as observed in murine studies, was not addressed in this study and will require further investigation.

The responsiveness of sclerotic skin manifestations in 1 patient treated with tocilizumab may provide some new insight into the pathophysiology of skin fibrosis during GVHD. Recent studies from Hill and colleagues [30] have demonstrated that cGVHD induced in mice after transplantation of granulocyte-colony stimulating factor (G-CSF)-mobilized stem cell grafts is associated with development of scleroderma in the skin. This was reportedly because of the overproduction of IL-17. IL-6 reportedly plays a pivotal role in the differentiation of T_H17 cells from naive T cells. Naive T cells stimulated with anti-CD3 and anti-CD28 antibodies in the presence of transforming growth factor-beta (TGF-β) differentiate into induced regulatory T cells, whereas exposure to IL-6 along with TGF-β drives them to become T_H17 cells capable of secreting IL-17 [31,32]. Thus, blockade of IL-6 may serve to decrease differentiation of naïve T cells into T_H17 cells and thereby attenuate skin sclerosis. Alternatively, reported effects of tocilizumab on the memory B cell compartment [33] is another mechanism by which this agent may have facilitated a response, given the role that B cells play in cGVHD [13]. Notably, anti-IL-6 therapy reportedly suppresses procollagen production in fibroblasts from scleroderma patients [34]. A recent report has also demonstrated alleviation of fibrotic skin changes in a small group of patients with primary scleroderma treated with tocilizumab [35]. Collectively, these data point to a role for IL-6 in the fibrosis and sclerotic skin changes that can occur as a consequence of cGVHD, and suggest that blockade of IL-6 may represent a novel treatment approach for this complication.

Adverse events associated with tocilizumab administration were consistent with those previously reported for this agent [22,23,36,37] and those typically observed in allogeneic transplant recipients (eg, infections). There were elevations in serum transaminases in several patients, but these tended to be modest and did not increase with subsequent infusions. One patient required a liver biopsy because of hyperbilirubinemia, which worsened to grade 4 after initiation of tocilizumab. The biopsy showed no evidence of GVHD or CMV hepatitis, with only cholestasis noted on pathologic examination. The cause of her hyperbilirubinemia remained undetermined, and it was uncertain the extent to which tocilizumab may have contributed to this abnormality. Infections were the major concurrent event observed in many of these patients. It was difficult, however, to determine whether tocilizumab may have predisposed patients to infectious complications because all of these patients had recently received multiple modalities for their GVHD treatment and were all still taking other immune suppressive medications at the time of tocilizumab administration. All patients who were seropositive for CMV reactivated this virus posttransplantation. However, 3 of these 4 patients had CMV viremia that antedated tocilizumab administration. One died within 10 days after tocilizumab was begun with refractory GVHD. In the remaining 2 patients, viremia persisted for several months despite continuous anti-CMV therapy, but none developed CMV disease and eventually viremia cleared in both patients. The fourth patient developed CMV colitis post-tocilizumab administration. The remaining infections that were observed in this cohort of patients were either bacterial or fungal in origin.

The tocilizumab dose administered in this study was based on prior experience derived from the use of this agent in adult patients with rheumatoid arthritis [22]. In that report, a dose of 8 mg/kg was found to be superior to 4 mg/kg when assessed at 3 months. For that reason, all patients were initially treated at that dose, although responding patients who remained on immune suppressive medications were dose reduced to 4 mg/kg in an effort to minimize exposure to another immunosuppressive agent. We also employed an administration schedule that was derived from prior clinical arthritis studies where tocilizumab was given approximately every 4 weeks. Although we were able to document clinical responses in patients with steroid-refractory GVHD, we do not know if this is the optimal schedule. Prior studies have shown that intravenous innunoglobulin has a much shorter half-life in bone

marrow transplant recipients when compared with normal controls [38]. Thus, it is possible that a more frequent administration schedule might be more clinically efficacious. In that regard, a recent study in patients with Crohn's disease, where tocilizumab administration showed remission-inducing activity, was given on an every 2 week basis [39]. Further studies will be needed to define this question.

In summary, these results demonstrate that tocilizumab has activity in the treatment of steroid refractory GVHD. The response observed in patients with lower GI tract involvement coupled with preclinical studies showing protection from GVHD within the colon microenvironment suggests that blockade of IL-6 signaling may represent a novel approach for the prevention and/or treatment of GVHD within this tissue site. Additionally, tocilizumab may also provide benefits in the therapy of skin sclerosis that occurs as a consequence of cGVHD. Tocilizumab was generally well tolerated, although whether this therapy predisposes patients to opportunistic infections remains to be determined. We conclude that further investigation of this agent in patients with both aGVHD and cGVHD is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient Characteristics

UPN	Age/Sex	Disease	CMV Serostatus (Donor/Recipient)	Type of Transplant	Conditioning Regimen	Acute GVHD Prophylaxis
2031	41/M	MM	Neg/Neg	Nonmyeloablative, matched related	TBI 200 cGy	Tacrolimus, MMF
2090	55/M	MM	Neg/Pos	Nonmyeloablative, matched related	TBI 200 cGy	Tacrolimus, MMF
2200	53/M	MM	Neg/Neg	Nonmyeloablative, matched related	TBI 200 cGy	Tacrolimus, MMF
2272	52/M	CLL	Neg/Pos	Myeloablative, matched unrelated	TBI 1200 cGy Cyclophosphamide	Tacrolimus, MMF
2292	52/M	MM	Neg/Pos	Nonmyeloablative, matched unrelated	Fludarabine, TBI 200 cGy	Tacrolimus, MMF, rapamycin,
2496	42/F	AML	Neg/Neg	Myeloablative, mismatched unrelated	Busulfan, cyclophosphamide	ATG, tacrolimus, methotrexate
2502	67/F	CLL	Neg/Neg	Nonmyeloablative, matched unrelated	Fludarabine, TBI 200 cGy	Tacrolimus, MMF
2503	40/F	AML	Pos/Pos	Myeloablative, mismatched unrelated	Busulfan, cyclophosphamide	ATG, tacrolimus, steroids

MM indicates multiple myeloma; CLL, chronic lymphocytic leukemia; AML, acute myelogenous leukemia; TBI, total body irradiation; MMF, mycophenolate mofetil; ATG, antithymocyte globulin.

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2013 July 19.

Table 2

GVHD Characteristics

UPN	Onset of GVHD (Day Post-BMT)	Overall Stage of GVHD	Organ Involvement (Stage)†	GVHD Therapy before Tocilizumab‡	Tocilizumab Administration (Day Post-BMT)
2031	724*	Classic chronic	Skin sclerosis, joint contractures	Steroids, photopheresis, gleevec, plaquinel	984
2090	142	IV	Gut (IV)	steroids, infliximab (4), campath (2), MMF, budesonide, octreotide	184
			Liver (III)		
2200	487*	Classic chronic	Skin sclerosis, joint contractures	Steroids, photopheresis, infliximab, gleevec, sirolimus, lidocaine, campath (10), rituxan (4), MMF, PUVA, plaquinel	669
2272	26	IV	Skin (IV)	Steroids, photopheresis	39
2292	106	II	Gut (II)	Steroids, infliximab (4), budesonide, tacrolimus	235
2496	23	IV	Skin (II)	Steroids, infliximab (2), budesonide	51
			Gut (IV)		
2502	52	IV	Skin (II)	Steroids, infliximab (3)	82
			Gut (IV)		
2503	24	IV	Skin (II)	Steroids, MMF	32
			Gut (IV)		

MMF indicates mycophenolate mofetil; BMT, bone marrow transplant; GVHD, graft-versus-host disease.

*Denotes onset of chronic GVHD in these 2 patients.

†Gut involvement in these patients was all lower tract disease.

‡Number in parentheses indicates total number of infusions given of infliximab, campath, or rituxan.

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2013 July 19.

Table 3

Clinical Outcomes and Immune Suppressive Therapy*

UPN	Response (Day 56)	Current Status	Cause of Death	Pre-Tocilizumab Therapy	Post-Tocilizumab Therapy†
2031	Stabilization of skin sclerosis	Alive, d+1123	—	Prednisone 30 mg every day, gleevec, rapamycin, photopheresis	Prednisone 20/10 every other day, rapamycin, photopheresis, plaquenil
2090	NE	Dead, d+195	GVHD	NA	NA
2200	PR	Alive, d+752	—	Prednisone 10 mg every day, rapamycin, gleevec, lidocaine, photopheresis every 2 weeks	Prednisone 10 mg every other day, photopheresis every 6 weeks
2272	PR	Dead, d+213	Infection	SoluMedrol 65 mg twice a day, tacrolimus	Prednisone 30 mg every day
2292‡	CR	Alive, d+496	—	SoluMedrol 10 mg every day, tacrolimus, MMF, budesonide	Hydrocortisone 20/10 mg every day, budesonide
2496	CR	Alive, d+174	—	SoluMedrol 50 mg every day, MMF, budesonide	Prednisone 20 mg every day, budesonide
2502	PR	Alive, d+157	—	SoluMedrol 50 mg twice a day, MMF 1 g twice a day, tacrolimus	SoluMedrol 30 mg every day, MMF 750 mg twice a day, tacrolimus
2503	NR	Dead, d+85	GVHD	NA	NA

NE indicates not evaluable; CR, complete response; PR, partial response; NR, no response; NA, not applicable; GVHD, graft-versus-host disease.

*Immune suppressive therapy pre- and post-tocilizumab is shown for responding patients only.

†Post-tocilizumab therapy refers to the immune suppressive regimen that each patient was taking at the time of last contact.

‡Post-tocilizumab steroid dose in this patient was replacement therapy to prevent adrenal insufficiency.

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