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DIAGNOSTICS AND ENVIRONMENTAL FACTORS

Tocilizumab-induced neutropenia in rheumatoid arthritis patients with previous history of neutropenia: case series and review of literature

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Abstract One of the adverse events of tocilizumab (TCZ) is a transient, dose-dependent neutropenia. The recommendations of the Summary of Product Characteristics state that this neutropenia should be managed according to the absolute neutrophil count (ANC). However, the approach to a patient who had a history of neutropenia induced by previous DMARDs and developed TCZ-induced neutropenia remains unclear. We would like to report a series of four patients with rheumatoid arthritis who developed Grade 2 neutropenia (ANC 1–1.5 $\times$ 10^9/L) following intravenous TCZ treatment at a dose of 8 mg/kg. All of them had a previous history of neutropenia (Grade 2 or Grade 3) due to Etanercept (three patients) and Sulfasalazine (one patient). Therefore, we decided to decrease the TCZ dosage by 10–20 % approximately. Reducing of the dosage did not have any influence on the efficacy of TCZ, and all of our patients remained in clinical remission. The mechanisms underlying neutropenia induced by Tocilizumab, Etanercept and Sulfasalazine are also discussed in this article.

Keywords Tocilizumab · Rheumatoid arthritis · Neutropenia

Introduction

Tocilizumab (TCZ) is a humanized monoclonal antibody against IL-6 receptor that provides a well-established treatment for the management of rheumatoid arthritis (RA). The safety profile of TCZ in clinical trials has been proven to be good, with adverse events rate similar to control groups. One of the well-known adverse events of TCZ is transient, dose-dependent neutropenia [1–3] that is probably caused by the inhibition of the biologic effect of IL-6 on the recruitment of neutrophils into the peripheral blood [3–6].

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The meta-analysis of six trials and five long-term extensions demonstrated that Grade 3 neutropenia (ANC 0.5–1 $\times$ 10^9/L) and Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) were observed in 6 % of the patients approximately [5].

Grade 1 neutropenia (ANC 2–1.5 $\times$ 10^9/L) and Grade 2 neutropenia (ANC 1.5–1 $\times$ 10^9/L) were found more frequently and reported in 15 % of patients [5]. No correlation between low ANC and the incidence of infection was established in this meta-analysis and in other published reports [5, 7–9].

The Summary of Product Characteristics (SPC) does not recommend the initiation of TCZ in patients with a pre-treatment ANC below 2 $\times$ 10^9/L [7]. Additionally, according to the recommendations of SPC, the following dose adjustments are appropriate for patients on TCZ treatment: If ANC is higher than 1 $\times$ 10^9/L, the current dose should be maintained. Interruption of TCZ therapy is recommended when ANC is between 0.5 $\times$ 10^9/L and 1 $\times$ 10^9/L. The therapy may be restarted at a dose of 4 mg/kg when ANC level rises above 1 $\times$ 10^9/L, and if clinically required, the dose may be increased to 8 mg/kg afterward.

Also, TCZ treatment should be discontinued if ANC level drops beneath 0.5 × 10^9/L [7].

There is no clear approach to a patient who had a normal baseline ANC before TCZ administration and developed TCZ-induced neutropenia while having a history of neutropenia induced by previous immunosuppressive drugs.

We would like to report a series of four patients who developed Grade 2 neutropenia following IV TCZ treatment at a dose of 8 mg/kg, which improved after decreasing the TCZ dosage by 10–20 % without any influence on TCZ efficacy. All these patients had a previous history of drug-induced neutropenia secondary to Etanercept (3 patients) and Sulfasalazine (1 patient).

Case 1

A 52-year-old woman with seropositive erosive RA since 2000 was taken off Sulfasalazine, Methotrexate, Plaquenil and Infliximab due to intolerance and lack of efficacy. Etanercept was commenced in January 2013. In June 2013, her ANC dropped from the baseline level of 5.53 × 10^9/L–1.45 × 10^9/L and the drug was discontinued. Within two months, the patient's cell count recovered (ANC 2.5 × 10^9/L), but the disease worsened (DAS28 CRP 4.2). In October 2013, the patient started monotherapy with IV TCZ with a dosage of 8 mg/kg (720 mg) every four weeks. The result was a rapid clinical improvement during several weeks with complete resolution of arthritis. However, after 4 months of treatment, her ANC dropped to 1.4 × 10^9/L. Although the patient's neutropenia was only Grade 2, she had a history of Etanercept-induced neutropenia. Therefore, it was decided to decrease the TCZ dose to 600 mg every 4 weeks (a decrease of 16 % approximately), without waiting for a possible worsening of the neutropenia.

Two months later, the neutropenia resolved (ANC of 2.2 × 10^9/L) and TCZ dose was increased to the previous dose of 720 mg every 4 weeks, without affecting ANC level during the last 6 months of observation. It should be noted that since TCZ was started, the patient remained in clinical remission.

Case 2

A 57-year-old woman with an 11-year history of seropositive RA started IV TCZ at a dose of 8 mg/kg (520 mg) in October 2012 after failed treatment with Gold, Cyclosporine, Sulfasalazine, Methotrexate, Plaquenil, Infliximab, Etanercept and Adalimumab due to persistent arthritis. Furthermore, the failed treatment with Etanercept and Adalimumab led to Grade 2 and Grade 3 neutropenia, respectively. TCZ was added to Leflunomide (20 mg/day) and Prednisone (5 mg/day), and this resulted in clinical remission (DAS28 CRP decreased from 4.8 to 2.4). Her ANC before the introduction of TCZ was 2.2 × 10^9/L, but within 4 months, it dropped to 1.4 × 10^9/L. Therefore, the TCZ dosage was reduced to 400 mg (a decrease of 21 % approximately) every 4 weeks and the patient's neutropenia resolved. Four months later, TCZ dosage was increased to 520 mg every 4 weeks. Now, 4 months since the last change in the dosage, the patient remains in clinical remission with a stable ANC level of 3.4 × 10^9/L.

Case 3

A 57-year-old woman was diagnosed with seropositive RA in 1994. Her previous treatments included NSAIDs, Prednisone, Gold, Methotrexate, Leflunomide, Plaquenil and Infliximab. From 2005 to 2011, she was treated with Etanercept at a low dose of 25 mg every 6 days in addition to methotrexate 7.5 mg every week because of neutropenia which varied in this period between Grade 2 and Grade 3. She had a low disease activity with DAS 28CRP 3.2.

In 2012, the frequency of Etanercept injections decreased from once every 6 days to once every month due to neutropenia with ANC level of 1.3 × 10^9/L. However, because her disease became active and her ANC remained on the same level, Etanercept was put on hold in October 2012. Her baseline ANC on Methotrexate alone was within normal levels. In November 2012, IV TCZ with a dosage of 8 mg/kg (520 mg) was introduced with a rapid clinical response after the first infusion. Despite this fact, the treatment was stopped because the ANC level dropped to 1.4 × 10^9/L, and Methotrexate was also discontinued. In March 2013, TCZ was re-challenged at the same dose of 520 mg every 4 weeks after the normalization of the ANC level (2.36 × 10^9/L). The ANC level continued to be stable until August 2013, when it fell to 1.3 × 10^9/L. Then, the TCZ dose was reduced to 400 mg (a decrease of 20 %) every 4 weeks, and the patient was in clinical remission for 1 year with a complete resolution of neutropenia (ANC of 2.46 × 10^9/L).

Case 4

A 64-year-old woman with seropositive RA since 2006 was treated with Methotrexate at a dose of 12.5 mg per week, along with Sulfasalazine and oral Prednisolone at doses of 1 gram and 5 mg per day, respectively. In July 2012, she was taken off Sulfasalazine due to neutropenia with ANC of 1.4 × 10^9/L. This leads to an improvement in regard to her ANC, which reverted to the baseline level of 2.8 × 10^9/L. However, after 4 months, her disease became active with DAS28 CRP 5.2.

In January 2013, the patient began TCZ at a dose of 8 mg/kg (440 mg) every 4 weeks with an excellent clinical response. Yet, in August 2013, her ANC dropped to 1.45×10^9/L and the dosage of TCZ was reduced to 400 mg (a decrease of 10 %), which led to the resolution of neutropenia within 2 months (ANC of 2.98×10^9/L). She remained in clinical remission during all this period (at present 18 months).

Discussion

We describe a series of four RA patients who developed Grade 2 neutropenia following TCZ treatment with a dosage of 8 mg/kg. Due to the fact that all these patients had a previous history of neutropenia associated with Etanercept or Sulfasalazine administration, we decided to decrease TCZ dosage by 10–20 % approximately. The temporal cause of neutropenia was associated with the administration of TCZ, and this was further confirmed when reducing the dosage of the drug led to the resolution of the neutropenia. For this reason, further hematological evaluation was not performed. In addition, none of the patients reported undercurrent illness that may have affected their neutrophil counts. Within the observation period following TCZ therapy, all our patients remained in clinical remission of RA, which lasted even though the doses of the drug were reduced.

Several reports of neutropenia induced by TNF-α blockers have been previously described [10–15], and the more severe cases of neutropenia are associated with Etanercept [11]. A recent retrospective study cohort of 367 patients with inflammatory arthritis demonstrated that 19 % of these patients became neutropenic with all three TNF-α blockers [15]. Another study showed that the main risk factor for neutropenia induced by TNF-α blockers is a previous history of neutropenia associated with commonly used DMARD's such as Methotrexate and Leflunomide [13].

There are controversial data regarding the question whether neutropenia induced by TNF-α blockers represents an individual drug adverse effect or a class adverse effect. On the one hand, there are several reports of neutropenia that resolved after switching to a different TNF-α blocker [11, 15]. On the other hand, our observation from Case 2 along with other observations demonstrated the recurrence of neutropenia after switching to another TNF-α blocker [10, 15].

The management of neutropenic episodes caused by TNF-α blockers consists of the following options: continuation of the original drug in cases of mild neutropenia, temporary cessation of the original drug and reinstatement once neutrophil count returns to normal level or switching to an alternative TNF-α blocker. Another option is modification of treatment by changing to other biologic DMARDs with a different pathophysiologic mechanism. In the mentioned above cases, we preferred this option and switched the treatment to TCZ.

Since our patients developed Grade 2 neutropenia after the initiation of TCZ as well, the following questions arise regarding the safety of TCZ: Is the risk of TCZ-induced neutropenia higher in patients with a previous history of neutropenia triggered by other DMARDs, specifically by Etanercept or Sulfasalazine? Is it necessary in this situation to wait until neutropenia escalates to Grade 3 before reducing the dose of TCZ? Are there similar pathophysiologic mechanisms responsible for neutropenia induced by TNF-α blockers, Sulfasalazine and TCZ?

To the best of our knowledge, there is only one report of a RA patient who was successfully treated with TCZ after Etanercept-induced pancytopenia [16]. In this case, the patient developed buccal ulceration, high-grade fever and severe pancytopenia 3 weeks after the initiation of Etanercept in addition to Methotrexate. It should be noted that the patient previously received Methotrexate alone, and his ANC was within the normal range. After the discontinuation of both drugs, the clinical presentations and the pancytopenia resolved. Afterward, TCZ was administered and achieved a complete remission of RA without any adverse effects. In order to understand the possible mechanism of this neutropenia, the apoptotic effects of TCZ and three TNF-α antagonists on peripheral blood mononuclear cells were evaluated. It has been found that in vitro, anti-TNF-α therapy induced a more significant apoptotic effect on peripheral blood mononuclear cells than TCZ. It has been suggested that all anti-TNF-α agents may induce apoptosis with a similar intensity in this patient who is apparently susceptible to the development of pancytopenia during TNF-α-blocking treatment. However, this observation is limited by the fact that the apoptotic effect of TNF-α blockers was evaluated on peripheral blood mononuclear cells. In this regard, it is more likely that the pancytopenia is caused by the effect of Etanercept on the bone marrow stem cells. Little is known concerning the choice of the preferred biologic therapy after an episode of severe neutropenia. However, this observation advocates that TCZ may be a safe treatment in patients with TNF-α blockers-induced neutropenia that is caused by an apoptotic effect and a possible bone marrow suppression [16].

Neutropenia has been similarly reported in some RA patients receiving Sulfasalazine. Bone marrow suppression (which may appear as leucopenia and neutropenia only) usually occurs within the first 3 months after the treatment is started.

In general, the mechanisms underlying the TCZ-induced neutropenia are not fully understood. Several different mechanisms of ANC decrease have been proposed, including bone marrow suppression, acceleration of peripheral apoptosis and margination of intravascular ANC.

The rapid occurrence of neutropenia that sometimes occurs within several hours following TCZ administration does not suggest an involvement of the bone marrow [17, 18]. In addition, this ANC reduction is not accompanied by suppressed production of other cells from the myeloid progenitor cells, such as basophils, eosinophils and monocytes.

Another possible explanation of TCZ-induced neutropenia is that TCZ may increase the neutrophil apoptosis. Apart from the case described above [16], the apoptotic effect of TCZ on neutrophils was evaluated in several additional studies. The most recent study investigated the interactions between IL-6, TCZ and neutrophils in vitro and in vivo [19]. It has been found that in vitro, TCZ did not have a significant effect neither on apoptosis nor on phagocytosis of apoptotic neutrophils by macrophages. It has been also found that IL-6 did not affect neutrophil apoptosis, and therefore, IL-6 depletion induced by TCZ cannot explain the neutropenia. Moreover, the protective antibacterial functions of neutrophils (apoptosis, respiratory burst and phagocytosis, and neutrophil surface molecule expression) were not affected in ex vivo neutrophils isolated from RA patients receiving TCZ [19].

Additional explanation for the neutropenia observed with TCZ may be a decrease in the circulating pool of neutrophils. It has been shown in animal models that IL-6 induces a rapid mobilization of neutrophils from the marginated pool to the circulating pool [3–6]. Therefore, it is possible that IL-6 blockage might actually shift neutrophils from the circulating pool (measurable by a complete blood test) to the marginal neutrophil pool.

Several studies have addressed themselves to determine whether neutropenia induced by TCZ is associated with increased risk for infection. Remarkably, these studies did not find a significant correlation between neutropenia and a higher rate of infection in patients with RA or Juvenile Idiopathic Arthritis [5, 7–9].

Conceivably, different mechanisms are responsible for TNF-α blockers, Sulfasalazine and TCZ-induced neutropenias in our patients and these events may be coincidental. On the other hand, a plausible explanation for neutropenia caused by TNF-α blockers and TCZ may be the shifting of neutrophils from the circulating pool to the marginal pool that may be induced by each drug.

The limitation of our observation is that we did not measure anti-neutrophil antibodies, and this may be an issue for further studies.

Conclusion

TCZ may be a safe treatment in RA patients with a previous history of neutropenia induced by Etanercept and Sulfasalazine. A temporary decrease in the TCZ dosage by 10–20 % approximately when TCZ-induced neutropenia reaches Grade 2 leads to the recovery of ANC without any influence on TCZ efficacy. Additional investigations are needed to clarify the mechanism of TCZ-induced neutropenia in patients with a history of neutropenia triggered by treatment with previous DMARDs.

Conflict of interest The authors have no conflicts of interest to declare.

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