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## Review Article

# Tocilizumab use during Covid-19 should alert an orthopaedic surgeon for the surgical management of arthroplasty patients: A narrative review

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## ABSTRACT

The crisis of Covid-19 has shaken the world healthcare systems. The intensive care resources to manage the medical conditions associated with Covid-19 are consistently found to be inadequate with exploration and implementation of newer treatment avenues for an early recovery. Presently, the use of Tocilizumab (TCZ) in severe to critical affection of Covid-19 is being practiced as an off-label therapy.

A narrative review of present knowledge regarding TCZ pharmacology, indications of its use, and potential side effects with clinical implications for an orthopaedic surgeon is presented. The article discusses the clinicopathological factors required to be monitored during the perioperative management of an orthopaedic patient who may have received TCZ for Covid-19 related illness.

The implications of its usage should alert the orthopaedic surgeons for future management of their arthritic surgical patients. The commonly associated side effects and complications in the post-operative phase following an arthroplasty or any orthopaedic surgery are an area of concern and considerable uncertainty. In the post-Covid-19 recovery phase, when surgeons need to plan a surgical intervention then a thorough evaluation of their Covid-19 medical management history may be warranted. Practical guidelines for the management of arthritic surgical patients have been postulated.

With an unregulated increased usage of TCZ during Covid-19 management, an orthopaedic surgeon should worry and needs to be aware of the possible consequences in the perioperative period for the post-surgery management. Future research to gain more insights will confirm the implied concerns.

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## 1. Introduction

“Failure will never overtake me if my determination to succeed is strong enough” by Og Mandino, should strengthen our resolve to develop our skills for fighting the Covid-19 pandemic.

The world healthcare systems during the crisis of the Covid-19 pandemic have explored unconventional management. The magnitude of the fatalities has shaken the established protocols. During the Covid-19 pandemic, scientists and researchers have applied emergency use authorization for off-label therapies.<sup>1</sup> This included

antiviral medications, convalescent plasma therapy, disease-modifying anti-rheumatic drugs (DMARD's) such as hydroxychloroquine for the initial management of the developing systemic affections due to the Covid-19 viral illness.<sup>1-3</sup> The rationale of use may be debatable however, a downward mortality trend encouraged the use.<sup>4</sup> Multiple continuing trials in different phases are underway to assess and evaluate rapidly accumulating scientific data for further authentication. However, this indiscriminate use of treatment modalities presents a dilemma for future developments for post-Covid-19 recovered individuals. The use of TCZ for rheumatoid arthritis (RA) and various autoimmune diseases has been researched, however for

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moderate to severe affections of Covid-19 the evidence is under trial.<sup>5</sup> The possible long-term impact of using TCZ in a subgroup of arthritic and spondyloarthropathy joint disorder patients recovering from Covid-19 raises an alarm for the orthopaedic surgeons. We review the literature regarding TCZ pharmacology, indications of its use and potential side effects with its clinical implications. We suggest few practical guidelines for an orthopaedic surgeon to implement for the management of Covid-19 recovered arthritic surgical patients. Future research will give more insights to confirm the implied concerns.

### 1.1. *Tocilizumab: Pharmacology and pharmacokinetics*

TCZ, a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1k subclass evidently binds to the interleukin-6 (IL-6) receptor, both the soluble and membrane-bound.<sup>6,7</sup>

IL-6, a pleiotropic cytokine, has a defined role in inflammatory responses and evidence support its role in biological processes including immune response regulation.<sup>8,9</sup> Involvement of IL6 in rheumatoid disease affection, the pathogenesis of RA, including increased expression of IL-6 in the synovium of patients with RA and a correlation between elevated IL-6 levels in serum or synovial fluid and measurements of the disease has been studied extensively.<sup>9–11</sup> IL-6 classic pathway is important for regenerative and protective function whereas the IL-6 trans-signalling pathway constitutes the pro-inflammatory activity of IL-6.<sup>12</sup>

In the pathogenesis of severe Covid-19, a cytokine storm occurs, involving the release of proinflammatory cytokines including IL-6, tumour necrosis factor (TNF- $\alpha$ ), and others.<sup>13–15</sup> TCZ inhibits the binding of IL-6 to its receptors and in doing so it reduces the cytokine's pro-inflammatory activity by competing with both the soluble and membrane-bound forms of the human IL-6 receptor.<sup>7</sup> As dysregulated IL-6 synthesis is thought to play a key role in this cytokine storm, similar to what happens in autoimmune diseases and malignancy, targeting IL-6 is a potential therapeutic approach for severe and critical Covid-19.<sup>16</sup>

### 1.2. *Tocilizumab: Indications and uses*

The orthopaedic surgeon, rheumatologist, and immunotherapist have explored its usage. TCZ has been used for the management of arthritis and autoimmune disorders following its introduction in Japan in 2008.<sup>17</sup> The use of TCZ was approved first for poor responders to DMARDs for the management of RA.<sup>17</sup> The European commission in 2009 further approved it for the management of moderate to severe active adult RA patients in combination with methotrexate (MTX) in patients who are intolerant and poor responders to TNF antagonists in addition to conventional

therapies with DMARDs.<sup>18</sup> The usage expanded to children over two years of age suffering from either systemic juvenile idiopathic arthritis or polyarticular juvenile idiopathic arthritis. Castleman's disease, a rare lymphoproliferative disorder involving plasma cell expansion was allowed for treatment with TCZ in Japan since 2005.<sup>6,7</sup> The use has been expanded to the treatment of autoimmune disorders though not yet licensed. The use of TCZ has been studied in diseases including Crohn's disease,<sup>19</sup> systemic lupus erythematosus,<sup>20</sup> Takayasu arteritis,<sup>21</sup> giant cell arteritis,<sup>22</sup> polymyalgia rheumatic<sup>23,24</sup> and refractory adult-onset Still disease.<sup>25–27</sup>

TCZ has shown promise in allogeneic hematopoietic stem cell transplantation patients against Chronic graft-versus-host disease affecting survival.<sup>28</sup> Further evaluation trials are under process. The use in kidney and liver transplant patients has been studied too.<sup>29</sup> The therapeutic potential of TCZ is being explored for the management of new-onset refractory status epilepticus refractory to rituximab immunotherapy.<sup>30</sup>

### 1.3. *Tocilizumab in Rheumatoid arthritis*

RA is a chronic systemic autoimmune disorder affecting approximately 0.5–1% of the population. The inflammation seen in RA is in part secondary to proinflammatory cytokines such as TNF alpha and interleukins such as IL-1 and IL-6. Treatment aims to attain low disease activity. A 20% improvement in tender or swollen joint counts, criteria defined by the American College of Rheumatology (ACR) is referred to as the ACR20 response.<sup>31</sup> The trials normally measure the primary outcomes of ACR20 as improvement of patients. An improvement of at least 70% translates to a very good response.

TCZ has strong therapeutic potential for the treatment of RA as demonstrated by review and meta-analysis study results.<sup>5,32</sup> Encouraging results with monotherapy has been one of the biggest advantages from a clinical and economic standpoint.<sup>31</sup> The additional advantages of TCZ including monthly frequency of administration, subcutaneous route of administration and relatively good safety profile, make it a reasonable option for patients with RA in approved dosages of 8 mg/kg every 4 weeks.<sup>5</sup>

### 1.4. *Tocilizumab use during Covid-19 pandemic*

The World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 outbreak a pandemic on March 11, 2020.<sup>33</sup> The viral illness has myriad symptoms and affection may vary from being an asymptomatic to a severe or critical illness. The recommendation for the use of TCZ as an off-label treatment during the phase of cytokine storm in Covid-19 to reduce and control the severity of affection have been discussed with variable response to the reduction in

mortality and effectiveness to control the cytokine storm following its use.<sup>34–36</sup>

IL-6 levels have been described to increase and then decrease in most patients after starting the TCZ therapy. The explanation is that the binding of TCZ to the IL-6 receptor inhibits receptor-mediated clearance of IL-6, leading to its accumulation in serum. A later decrease of IL-6 by interfering with the stimulus for the exaggerated immune response might result in stabilization or improvement of clinical outcome.<sup>34</sup> C-reactive protein (CRP) has been reported to decrease rapidly in patients treated with TCZ for Covid-19 and might help to predict outcomes soon after the treatment.<sup>16,34,35,37</sup>

WHO-approved double-blinded randomized controlled trial (RCT) was unable to give any conclusive evidence to support its efficacy in the management of severe to critical Covid-19.<sup>38</sup> However, data from meta-analysis for TCZ as a treatment option for severe and critically ill Covid-19 patients suggest that it reduces the mortality events, especially when prognostic factors in such patients have CRP level which is more than 100 mg/L and when PaO<sub>2</sub>:FiO<sub>2</sub> ratio (P/F ratio) is 200–300 mmHg, and/or <200 mmHg.<sup>39</sup> Studies for more meaningful results and assessment of optimum dosing have been further suggested.

### 1.5. *Tocilizumab effect in Peri-operative period*

RA patients under TCZ treatment may require to undergo an arthroplasty or orthopedic surgery. In a patient on TCZ infusion, Japan College of Rheumatology (2009) has formulated guidelines and advised to postpone surgery for at least 14 days after the last infusion.<sup>40</sup> The duration was variable and individualized. The TCZ infusion was withheld for a more prolonged duration of few more weeks ranging from four to six weeks, before planning for any surgical intervention. Though a long rest period before surgery was recommended, it has been more desirable in patients presenting with rheumatoid complications, in elderlies, and those on high doses of steroids.<sup>40,41</sup> The re-initiation of therapy is recommended soon after the surgery once the postoperative recovery is good with sound wound healing and in absence of any surgical site infections (SSIs).<sup>40,41</sup> A delayed re-initiation may flare up the symptoms.<sup>41</sup> The rheumatoid flare-up has been defined as the reappearance of arthralgia and swollen joints after surgery on a subjective patient assessment and is an unpleasant postoperative entity. The serological markers during the perioperative period become unsuitable for measuring the flared-up disease activity.<sup>41</sup>

Un-like other conventional DMARDs or TNF blockers, the postoperative incidence of increase in CRP and rise of temperature do not occur significantly in most cases even after major surgery, especially when the duration from final infusion to surgery was short.<sup>41</sup> In a retrospective pair-matched case-controlled study, evaluation was done

for acute-phase responses in RA patients treated with TCZ and who underwent arthroplasty procedures.<sup>42</sup> The authors concluded that operations can be performed safely on patients during TCZ treatment. In their small series of 22 patients, they observed that TCZ suppressed fever and increase of CRP in the immediate post-operative period. The plausible cause considered was due to inhibition of IL6 which suppressed the systemic inflammatory manifestations of RA. However, there was no influence on the whole blood count (WBC), neutrophil, and lymphocyte counts.<sup>42</sup>

### 1.6. *Tocilizumab: Side effects and complications*

Infections were the most common adverse events in the majority of TCZ treated RA patients.<sup>32</sup> However, serious infections were uncommon (1–8%). The incidences of cellulitis, upper respiratory tract infection, pneumonia, abscesses, septic arthritis, osteomyelitis, and polyarthritis have been reported. Increased chances of infections are expected when using an immune-suppressive agent. No opportunistic infections or cases of tuberculosis infections or activations were reported in any of the RCTs for TCZ.<sup>32</sup>

Operated patients with underlying RA have an otherwise increased risk for the SSIs infections as compared to the general population.<sup>43–45</sup> The susceptibility to infections is higher in RA patients on management with biological agents.<sup>46</sup> In immediate postoperative period the neutrophil and lymphocyte counts were significantly decreased following a TCZ administration.<sup>47</sup> To detect early postoperative SSIs monitoring of body temperature, CRP level, and WBC, as well as local findings need consideration as indicators for infection.

Many basic studies have reported that IL-6 plays a role in wound healing, and many investigators think that IL-6 modulates immune responses and is essential for timely wound healing.<sup>48,49</sup> TCZ in perioperative period (TOPP) study was a multicenter study analyzing perioperative clinical features and complications after orthopaedic surgery in RA patients treated with TCZ in a real-world setting.<sup>41</sup> An increased incidence of approximately 12.4% for delayed wound healing which is higher than general population was observed in foot and spinal surgeries.<sup>41</sup> However, no increased complications of superficial or deep infection or delay in wound healing after orthopaedic surgery were observed in another study.<sup>42</sup>

A potential cardiovascular risk due to increased lipid levels subject to anti-inflammatory activity warrants observation. Increased liver enzymes when used in combination with MTX, is an area of concern though the drug-induced hepatitis is not known with TCZ.<sup>6,31</sup> Gastrointestinal disturbances and neutropenia are few relevant other concerns. Thrombotic events and visual complications need close observations.<sup>36</sup>

### 1.6.1. Key points to guide

The orthopaedic surgeon should be worried when dealing with arthritic surgical patients with history of recovery from severe to critical Covid-19 illness.

1. A careful pre-operative planning with detailed history taking should guide decision making. Inquire regarding the use of therapeutic drugs, their dose and duration of medications used, the length of intensive care and/or hospital stay, and the assessment of clinical course during hospitalization.
2. Evaluation of pro-inflammatory markers including CRP should guide regarding the recovered phase for Covid-19 and additional evaluation for the risk assessment for infection.
3. Preoperative assessment of skin conditions for possible wound complications should be done. Meticulous closure of wounds to be done, especially in patients undergoing spine and foot surgery to reduce the risk of delayed wound healing.
4. The masking effect of TCZ in RA in the postoperative period should alert the surgeon in RA patients undergoing arthroplasty. In the immediate postoperative period, there may be normal temperature and normal CRP if the duration from the last TCZ infusion is short. Close monitoring for evidence of infections in postoperative period seems appropriate.
5. TCZ use during Covid-19 management along with narrow therapeutic window medications such as theophylline, phenytoin, warfarin, cyclosporine may need monitoring even after discontinuation for at least 1-2 months as TCZ has a long half-life.<sup>50</sup> The concurrent use with anticoagulant therapeutic drugs may lead to more chances of thrombosis. Cautious use with TNF- $\alpha$  inhibitors, omeprazole and simvastatin is also suggested.<sup>50</sup>
6. The re-initiation of TCZ infusion postoperatively should not be delayed as it may flare up rheumatoid symptoms. According to the ACR/AAHKS Guidelines for Perioperative Management for TCZ, the withhold time was based on the mode of administration. The dosing interval for the subcutaneous mode of TCZ is every week; the schedule surgery time is week 2. The dosing interval for the intravenous mode of TCZ is every four weeks, the schedule surgery time is week 5.<sup>51</sup> Though, it may need to be individualized based on wound healing, assessment for infections, and postoperative general condition assessment.

## 2. Conclusion

With the increased use of TCZ during Covid-19, an orthopaedic surgeon's awareness of the perioperative conditions and strict monitoring of pro-inflammatory parameters will help to avoid complications. Future studies

will give further evidence to confirm and define the role of TCZ in the management of Covid-19, however, the orthopaedic surgeon needs to know and be prepared for the management of Covid-19 recovered arthritic surgical patients.

## 3. Abbreviations

TCZ: Tocilizumab, DMARD's: Disease-modifying anti-rheumatic drugs, RA: Rheumatoid arthritis, IL-6: Interleukin-6, TNF- $\alpha$ : Tumour necrosis factor, WHO: World Health Organization, CRP: C-reactive protein, RCT: Randomized controlled trial, MTX: Methotrexate, ACR: American College of Rheumatology, SSIs: Surgical site infections, WBC: Whole blood count.

## 4. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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