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The implications of biologic therapy for elective foot and ankle surgery in patients with rheumatoid arthritis

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HIGHLIGHTS

- There are British Society for Rheumatology (BSR) guidelines for the peri operative management of patients on anti-TNF therapy and Tocilizumab.
- There are no BSR guidelines for the other biologic agents.
- The BSR suggests anti-TNFα therapy is stopped 3–5 times the half-life of the drug whilst Tocilizumab is stopped 4 weeks prior to surgery.
- Local pathways may vary from the BSR recommendations with regards to continuing or stopping biologic therapy prior to foot and ankle surgery.

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is one of a number of inflammatory arthropathies resulting in foot pain and deformity. Patients with this disease may require surgical intervention as part of their management. Many of these patients are now taking biologic agents which pose several risks to patients in the perioperative phase. The surgical team therefore need to be aware of these associated complications and how to manage these cases.
Aim: This paper aims to review the current literature about perioperative needs (foot and ankle surgery) associated with patients with rheumatoid arthritis receiving biologic therapy.
Main findings: The majority of the literature discusses the perioperative complications associated with patients on anti-TNFα therapy with few studies investigating the other biologics in common use. There is conflicting evidence as to the safety of continuing or stopping biologic drug therapy prior to orthopaedic procedures. The British Society for Rheumatology (BSR) have produced guidelines for the management of patients on anti-TNFα therapy or the biologic agent Tocilizumab. These recommendations suggest the risks of post-operative infection need to be balanced against the risk of a post-operative disease flare. In essence, it is suggested anti-TNFα therapy is stopped 3–5 times the half-life of the drug whilst Tocilizumab is stopped 4 weeks prior to surgery.
Conclusion: Good communication is needed between the surgical team and the local Rheumatology department managing the patient's disease in order to optimise perioperative care. Local pathways may vary from the BSR recommendations to determine the most suitable course of action with regards to continuing or stopping biologic therapy prior to foot and ankle surgery.

1. Introduction

Rheumatoid arthritis (RA) is one of a number of inflammatory arthropathies which can result in debilitating foot pain and deformity [1]. It is an auto immune inflammatory disease, characterised by chronic synovitis and progressive joint damage [2]. The incidence of RA in the UK is estimated to be 0.025–0.05%, with a prevalence of 1.2% in females and 0.4% in males [3]. Of those newly diagnosed, 16% of patients have foot involvement however, there is some notable variation within reported estimates [4]. As RA disease progresses the number of patients with symptomatic feet rises to a reported 90% and the prevalence of fixed deformity also notably increases [5]. The National Institute for Health and Clinical Excellence (NICE) guidelines suggest early referral for a specialist surgical opinion when pain, function or deformity fail to respond to optimal non-surgical management [6]. Since the publication of

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this guidance, an increasing number of patient symptoms are managed pharmacologically with biologic agents. Thus, an increasing number of patients with RA, who are in receipt of biologic therapy, are likely to present for a foot and ankle surgical opinion. Currently however, there is limited data highlighting their safety in relation to surgical intervention [7]. The aim of this paper is therefore to review the current literature about perioperative needs (foot and ankle surgery) associated with patients with rheumatoid arthritis receiving biologic therapy.

2. Pharmacological management of RA

Disease modifying anti-rheumatic drugs (DMARD's) are the cornerstone for drug management of this auto-immune disease with methotrexate indicated as first line treatment [6]. In patients who fail to respond to at least two conventional DMARD's, TNF inhibitors may be considered [8]. The table below highlights the various inflammatory inhibitors used in the management of RA [9]: (Table 1).

3. Pre-operative assessment

When considering the surgical management of these patients, careful consideration needs to be made as to the overall disease state. This will allow appropriate surgical planning and optimum perioperative management where surgery is to take place. As well as a thorough systems evaluation the pharmacological treatment that patients may be taking needs to be considered. Patients with RA may be using corticosteroid therapy, non-steroidal anti-inflammatory drugs (NSAID's), disease modifying anti-rheumatic drugs (DMARD's) in addition to biologic therapy. The common side effects of these drugs should be considered at pre-operative assessment. Where long term corticosteroid therapy has been employed, equivalent to greater than 10 mg per day of prednisolone, patients may require steroid cover (*i.e.* supplementary glucocorticoids) due to the resultant adrenal suppression [10].

There is conflicting evidence as to the safety of continuing or stopping biologic drug therapy prior to orthopaedic procedures. The British Society for Rheumatology (BSR) has produced guidelines for the management of patients on anti-TNFα therapy or the biologic agent Tocilizumab. These recommendations suggest the risks of post-operative infection need to be balanced against the risk of a post-operative disease flare. In essence, it is suggested anti-TNFα therapy is stopped 3–5 times the half-life of the drug whilst Tocilizumab is stopped 4 weeks prior to surgery.

4. Post operative assessment

4.1. Infection

It has been suggested that patients receiving biologic therapy have a greater risk of post-operative infection [11]. Animal models looking at *Staphylococcus aureus* septic arthritis demonstrate early up-regulation of inflammatory cytokines including TNF-α [12]. Supporting these findings are reports of spontaneous infections in both native and prosthetic joints along with osteomyelitis in patients treated with anti-TNFα [13]. Furthermore another trial found that patients on anti-TNFα therapy had a two-fold increase in bacterial infections requiring hospitalisation compared to patients taking traditional DMARD's, although these findings were not specifically related to surgical acquired infections [14].

There are few other reported studies investigating the risks associated with discontinuation of biologic therapy in the perioperative phase in elective surgery or the resultant post-operative infection risk. Den Broeder et al. [15] found there was no statistical difference in post-operative complications when comparing patients who continued their biologic therapy compared to those who stopped prior to surgery [15]. They noted only 6 patients of 104 who continued anti-TNFα therapy had a surgical site infection compared with 8 patients out of 92 who discontinued their biologic. Whilst it can be inferred therefore that there is no significance difference in infection between groups it should be noted that the type of elective surgery compared in the final analysis was unclear and represent a confounding effect [16]. It is noteworthy that different types of surgery may carry different post-operative infection risk.

In contrast to the findings of Den Broeder et al. [15] another retrospective review found the risk of infections after elective surgeries was higher in patients who were treated with biologic agents during the peri-operative stage [17]. Looking at a total of 91 patients who underwent a variety of elective orthopaedic procedures the authors noted a significant increase in infection in those patients managed with biologic therapy ($p = 0.041$, OR 4.4, 95% CI 1.10–18.41) and additionally noted that this group were less likely to have undergone large joint primary arthroplasty. This difference in infection prevalence remained statistically significant after adjustment for age, sex, and disease duration (OR 4.6, 95% CI 1.1–20.0); prednisone use, diabetes, and serum rheumatoid factor status (OR 5.0, 95% CI 1.1–21.9); and all 6 variables simultaneously (OR 5.3, 95% CI 1.1–24.9) [17].

A recent matched case control study compared complication rates between 49 patients (69 surgical procedures) on TNF inhibitors and 63 patients (64 surgical procedures) on conventional DMARD's [11]. Patients on Adalimumab were excluded from this study. In the anti-TNFα group, drug therapy was discontinued in the peri-operative phase as per both the British Society of Rheumatology and Japanese College of Rheumatology recommendations. The paper did not specify whether or not conventional DMARD's were continued or discontinued. The authors found the anti TNFα group had a significantly higher risk of surgical site infection (SSI). These conclusions were however challenged by Backhouse et al. [18] who identified that both the definition of a SSI along with the methodology potentially led to false conclusions. It is noteworthy that the surgeons were not blinded regarding which patients continued anti TNF therapy and given the potential increased risk of infection associated with this group, the surgeons may have had a higher index for suspicion of infection and lower threshold for prescribing antibiotics. Additionally, in all instances where antibiotics were provided (either prophylactically or otherwise), this was considered as indicative of infection, and may therefore represent an overestimation of infection prevalence [18]. Similar comparative prevalence of infection between treated and un-treated groups ($N = 22$) were also reported by Hirao et al. [19], in an evaluation of Tocilizumab and Godot et al. [20] in an evaluation of Rituximab. However, the sample for both works is limited and not statistically powered to demonstrate significant effect. To date, there seems to be relatively little evidence therefore to conclusively demonstrate increase post-operative infection prevalence in patients managed with any biologic therapy.

Table 1
Biologic therapy for rheumatoid arthritis.

Drug name	Mode of action
Adalimumab	Inhibit activity of TNF-α
Certolizumab pegol	Inhibit activity of TNF-α
Etanercept	Inhibit activity of TNF-α
Golimumab	Inhibit activity of TNF-α
Infliximab	Inhibit activity of TNF-α
Rituximab	Anti CD20 antibody (B cell)
Abatacept	Prevents full activation of T-Lymphocytes
Anakinra	Inhibits activity of interleukin-1
Tocilizumab	Antagonises action of interleukin-6