Managing rheumatoid arthritis during COVID-19

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Abstract
The outbreak of coronavirus in the world has led to an uncertainty about treatment of patients with autoimmune disorders because of their weakened immune system coupled with immunosuppressive agents they take which predisposes them to a host of infections. Data on COVID-19 patients with underlying rheumatological diseases has been emerging mostly in the form of small case series and one global registry. From these data, it seems like our patients, although immunosuppressed, are not particularly susceptible to the coronavirus infection and if infected, do not have significantly worse outcomes than other patients. In fact, drugs like hydroxychloroquine, dexamethasone, and tocilizumab have been studied for treatment of COVID-19. However, this is only preliminary data, and since a few parts of the world are still grappling with the pandemic at its peak, we need to be equipped on how to protect and manage our immunosuppressed patients. Published evidence to guide treatment decisions are lacking and doubts regarding continuation and initiation of immunosuppressants remain. Rheumatoid arthritis (RA) is the most common immune-mediated disorder in COVID-19 patients, and in this review, we discuss how the commonly used drugs in RA alter the patients’ susceptibility to this infection. The review also summarizes the recommendations from the major bodies on how to manage this disease in these times.

Keywords COVID-19 · Management · Rheumatoid arthritis · Treatment

Introduction
The outbreak of coronavirus infection throughout the world is a matter of global emergency. Patients with comorbidities, in their old age, and with a compromised immune system are at the highest risk of mortality. Patients with autoimmune diseases, like lupus and rheumatoid arthritis (RA), already have a compromised immune system which is coupled with the prescribed immunosuppressive agents they take—making them more susceptible to infections. Patients on immunosuppressants may present atypically; for example, patients on steroids may not mount a febrile response and patients on IL-6 inhibitors may not have a rise in inflammatory markers [1]. Another clinical challenge which may present while treating RA patients is the overlap of symptoms which may occur between the flare of RA and COVID-19 infections. Symptoms like myalgia, arthralgia, fever, and elevated inflammatory markers may occur in both cases. An exacerbation of RA-associated Interstitial Lung Disease (RA-ILD) can mimic symptoms of COVID-19 infection. COVID-19 testing by real-time polymerase chain reaction (RT-PCR) should be used to differentiate the two cases in such scenarios. In a retrospective study done to analyze the clinical characteristics of COVID-19 infections in patients with and without ILD, ten out of 28 patients with ILD had connective tissue disease-ILD. A higher proportion of patients with ILD presented with...
cough, dyspnea, diarrhea, fatigue, neutrophil and monocyte counts, interleukin-8, 10, 1, and D-dimer levels as compared with patients without ILD [2]. Although there is currently no evidence to prove that patients with autoimmune disorders or on immunosuppressive drugs are at a greater risk of contracting the COVID infection, there remains a theoretical risk of increased complications in such patients if they acquire the infection [3]. However, data from the COVID-19 Global Rheumatology Alliance Global Registry which gives live time information regarding rheumatic diseases and COVID-19 showed that as of on 17 August, 2020, the commonest rheumatic disease in which COVID-19 was documented was RA (694 patients out of 1783) [4]. Based on a few other studies, rheumatoid arthritis seems to be the most common rheumatic disease in which COVID-19 infection has been documented [3, 5]. In a Chinese case series of 5 patients with rheumatic diseases who developed COVID-19, four of them had RA and one had systemic sclerosis. In another case series from New York, in which 86 patients with immune-mediated inflammatory diseases who contracted COVID-19 were studied, a high percentage of the admitted patients had RA [6].

Rheumatoid arthritis is one of the most common diseases a rheumatologist encounters in their practice. Individuals with rheumatic diseases are on immunosuppressive agents and require special consideration in the COVID-19 era. An increased risk of infection in RA as compared with the general population has been documented. A prospective study on 2108 patients with inflammatory polyarthritis reported a two to four times increased risk of infections in those with history of smoking, steroid use, and positive rheumatoid factor [7]. Drugs used for treatment of RA like hydroxychloroquine and tocilizumab have been studied for treatment of coronavirus, while other drugs like corticosteroids render the patients grossly immunosuppressed and invite infections. In the current situation, where the end to this pandemic is not in sight, and information about treating our patients with a fragile immune system is scarce, the best strategy to manage them is unclear. Possibly, prevention of infection by regular hand washing, wearing masks, maintaining social distancing, and avoiding public areas remains the best advice one can offer. In this review, we will summarize the recommendations of various bodies for treatment of stable and active RA during COVID-19 and analyze the drugs used for its treatment: whether their use predisposes a patient to the infection and how their use should be altered in the current COVID-19 situation (Table 1).

Control of disease activity Control of disease activity is of utmost importance in this situation as studies have shown that high disease activities correlate with increased risk of acquiring infections. A study done by Accortt et al. showed the increase in incidence of serious infections in a group of RA patients with moderate to high disease activity as compared with that of patients with low disease activity and those in remission [8]. Data taken from the CORRONA (Consortium of Rheumatology Researchers of North America) registry also showed that with a 0.6 unit increase in Disease Activity Score-28 (DAS-28), there was a 4% increase in the rate of outpatient infections and a 25% increase in the rate of infections requiring hospitalization [9]. In the case series from China in which four RA patients were infected with COVID-19, the two patients who progressed to develop severe disease had not been on therapy prior to admission. However, the status of their disease activity was unknown [3]. In addition, acquiring infections can lead to a flare of RA warranting increase in immunosuppression, leading to a vicious cycle of infections and immunosuppressive therapy. Hence, control of disease activity is the first step in RA management during COVID-19.

Management of comorbidities RA patients have a documented increase in incidence of comorbidities like asthma, Chronic Obstructive Pulmonary Disease (COPD), hypertension, and cardiovascular diseases as documented in the COMORA study [10]. RA patients have an increased risk of diabetes as shown in a meta-analysis [11]. A study done on coronavirus-infected patients showed that presence of COPD, diabetes, hypertension, and malignancy were risk factors for admission to Intensive Care Unit, invasive ventilation, or death. The risk increased with increase in number of comorbidities [12]. Pre-existing respiratory illnesses, mainly COPD, was associated with increased severity of coronavirus infection [13]. Smoking, which is also associated with RA, appears to increase the risk of adverse outcomes in COVID-19 by increasing the expression of Angiotensin Convertase Enzyme (ACE) 2 in Asian current smokers [14, 15]. RA is also associated with ILD which might theoretically increase the risk of a severe infection but data on this is scarce. SARS-CoV-2 infects cells with ACE2 as a receptor, and the reduced infection rate of COVID-19 in patients with ILD has been proposed to be due to decreased angiotensin II mRNA activity in the lung in ILD. This same study stated that although the risk of infection might be lower in patients with ILD, once infected, the severity and prognosis are worse in patients with ILD due to aggravated inflammatory responses and coagulopathy [2].

The National Health Service (NHS) has classified patients of RA with and without ILD and Pulmonary Artery Hypertension (PAH) at a very high risk and increased risk respectively, for contracting the infection as compared with the general population [16]. Hence, management of comorbidities and extra-articular features of the disease is important in these times.

The demographic and clinical characteristics of the first 600 patients of rheumatic diseases who contracted COVID-19 were published recently. The data was taken from the COVID-19 Global Rheumatology Alliance (C19-GRA)
Physician registry. The most common rheumatic disease was RA (230, 38%) and the most common comorbidities were hypertension (199, 33%), lung disease including COPD, asthma, ILD, and others (127, 21%), diabetes, cardiovascular disease, and renal failure. Patients with comorbidities were more commonly admitted. However, no association between disease activity and hospitalization was seen [17].

Pharmacological management

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are often used in RA for relief of arthritis in acute settings. The World Health Organization (WHO) published a scientific brief about the use of NSAIDs in COVID-19 and stated that at present, there is no evidence of severe adverse events, acute health care utilization, long-term survival, or quality of life in patients with COVID-19 as a result of the use of NSAIDs. However, this data was acquired from patients with various acute viral respiratory illnesses, not specifically COVID-19 [18]. A review concluded that there is no conclusive evidence for or against the use of NSAIDs in COVID-19 currently [19, 20]. The C19-GRA data showed that NSAID use was reported significantly less frequently in hospitalized patients than non-hospitalized patients [17].

American College of Rheumatology (ACR) guidelines state that in active arthritis, NSAIDs may be initiated, but in patients with severe respiratory symptoms with documented or presumptive COVID-19 infection, NSAIDs should be stopped. In the absence of severe respiratory symptoms, the panel demonstrated low consensus with regard to stopping NSAIDs [21]. NICE guidelines and Australian Rheumatology Association recommend that patients taking NSAIDs for a long-term condition like RA can continue the same [1]. Considering the lack of clear evidence and possibility of ibuprofen exacerbating the infection, it might be prudent to avoid ibuprofen and use other NSAIDs during the pandemic.

Corticosteroids

Corticosteroids are the cornerstone of for managing disease flares and for initial treatment of RA as evidenced in the latest EUROpean League Against Rheumatism (EULAR) guidelines for RA management [22]. The disadvantage of corticosteroids is the increased risk of infections as documented in observational studies [23, 24]. A cohort study of over 15,000 patients over the age of 65 years with RA who were receiving Disease-Modifying Antirheumatic Drugs (DMARDs) identified glucocorticoids as a significant risk factor for bacterial infections. Glucocorticoid use doubled the rate of serious bacterial infections in a dose-dependent manner as compared with methotrexate, and no increased risk of bacterial infection was found among users of Tumor Necrosis Factor inhibitors (TNFi) [25]. Coupled with this is the increased incidence of comorbidities with long-term use of steroids which also predispose to increased severity of infections [26]. Initial studies performed on use of corticosteroids in COVID-19 concluded that there is no evidence to support its use in COVID-19, and it may in fact lead to more harm than good [27–29]. The interim guidelines of WHO also does not support the use of systemic corticosteroids for the treatment of viral pneumonia and Acute Respiratory Distress Syndrome (ARDS) for suspected COVID-19 cases [30]. However, the recently published preliminary report of the RECOVERY trial has brought about a radical change in the treatment of COVID-19 with respect to steroid use [31]. This study showed a lower 28-day mortality with low-dose dexamethasone (6 mg/day) use for 10 days in patients receiving either mechanical ventilation or oxygen as compared with those without respiratory support.

The British Society of Rheumatology (BSR) has stated that high-dose steroids > 20 mg/day for 4 weeks, and patients on lower dose of steroid in conjunction with another immunosuppressants constituted a very high-risk group for COVID-19 who require shielding [32]. The Global Rheumatology Alliance Global Registry data shows that out of 1783 patients with rheumatic diseases who contracted the COVID-19

| Drugs                     | Recommendation                                      |
|---------------------------|-----------------------------------------------------|
| NSAIDs                    | May be continued, consider stopping in severe infections |
| Steroids                  | Use lowest possible dose, avoid sudden discontinuation, low-dose dexamethasone in moderate to severe COVID-19 recommended |
| csDMARDs                  | May be continued; consider stopping SSZ, MTX, LEF in documented/presumptive COVID-19 |
| bDMARDs, tsDMARDs         | May initiate therapy in moderate to severe rheumatic conditions, withhold all biologics except IL-6 inhibitors in documented/ presumptive COVID-19 |
| Pneumococcal and influenza vaccine, vitamin D | Consider switching from intravenous to subcutaneous form if available |
|                           | Consider increasing dosing interval or reduction of RTX dose |

Table 1 Summary of recommendations from various guidelines regarding use of immunomodulatory therapy during COVID-19

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infection, 33.31% patients were on steroids [4]. Their published data showed that there was a significantly higher proportion of patients receiving high doses of glucocorticoids (> 10 mg/day) among those who were hospitalized than not hospitalized patients [17].

The NICE guidelines recommend not to stop corticosteroids suddenly in patients on a stable dose and to give parenteral steroids only in the presence of significant disease activity without other alternatives. They recommend a maximum of 0.5 mg/kg oral steroid for new onset polyarthritis [1]. ACR guidelines state that in presence of newly diagnosed or active arthritis, low-dose glucocorticoids may be initiated. They should not be stopped abruptly and the lowest possible dose to control the disease should be used [21]. The BSR recommends to only consider a steroid injection if a patient has high levels of pain and disability and has failed first-line measures (simple analgesia, activity modification, and splinting), and continuation of those symptoms will have a significant negative effect on their health and well-being and after obtaining informed consent. They recommend intraarticular injections only for active synovitis ± effusion and lowest clinically effective doses—maximum 40 mg methylprednisolone/triamcinolone acetonide for large joints and 20 mg for smaller joints and to avoid multiple site injections [33].

For patients on chronic steroids infected with coronavirus with high fever for many hours of the day, a higher dose is necessary. The Society for Endocrinology recommends that patients on 5–15 mg prednisolone daily should take 10 mg prednisolone every 12 h, and patients on oral prednisolone > 15 mg should continue their usual dose but take it split into two equal doses of at least 10 mg every 12 h [34].

**Conventional synthetic DMARDs**

Hydroxychloroquine has been shown in several studies to reduce the SARS-CoV viral load and reduce the duration of viremia. In vitro, chloroquine has been shown to be highly effective in control of COVID-19 infection by preventing SARS-CoV-1 from infecting the glycosylation of a virus cell surface receptor, ACE2 [35]. Multiple clinical trials have been conducted using hydroxychloroquine in COVID-19 patients. A clinical trial compared 20 patients with COVID-19 who received hydroxychloroquine with or without azithromycin with 16 controls and found that 70% demonstrated negative PCR on day 6 as compared with 12.5% in the control group. However, it was a non-randomized trial with a small sample size [36]. Concerns regarding cardiac arrhythmias arose when using this drug in combination with azithromycin, another drug potentially used against COVID-19, and other protease inhibitors. The Global Rheumatology Alliance Global Registry data shows that out of 1783 patients with rheumatic diseases with COVID-19, 26.4% patients were on hydroxychloroquine and 62.8% patients were on conventional synthetic DMARDs like methotrexate, sulfasalazine, and leflunomide [4]. In a New York case series, use of hydroxychloroquine and methotrexate was higher among hospitalized patients than ambulatory patients [6]. Nevertheless, because of the potential benefits of this drug, the Indian Council of Medical Research has recommended prophylaxis with hydroxychloroquine (400 mg twice daily for a day, followed by 400 mg once a week for 7 weeks) for healthcare workers dealing with COVID-19 as well as close contacts of these patients [37]. The Indian Rheumatology Association recommends that for positive cases, hydroxychloroquine may be started at doses of 800 mg on day one and 400 mg (not more than 5 mg/kg/day) from day two for another 5 days. Regimen should be started from day one of positively proven or day one of quarantine if testing is not done [38]. However, several studies published recently have shown that hydroxychloroquine is not effective and may even cause more harm than good. An observational study done in New York on 1376 patients, of which 58.9% received hydroxychloroquine, showed that the drug was not associated with a greatly lowered or increased risk of intubation or death [39]. In a retrospective cohort study of 1438 patients in New York, treatment with hydroxychloroquine, azithromycin, or both was not associated with significantly lower in-hospital mortality [40].

Antimalarial monotherapy and combination therapy with other DMARDs did not affect hospitalization status in the C19-GRA data [17]. Few studies have shown that patients on DMARDs are not at a risk for more adverse outcomes due to coronavirus [41, 42].

The NICE guidelines recommend temporarily stopping DMARDs other than hydroxychloroquine and sulfasalazine in patients known or suspected to have COVID-19 [1]. ACR guidelines state that in the absence of COVID infection or exposure, DMARDs can be continued. For patients well-controlled on hydroxychloroquine, it should be continued, if not available, switching to a different csDMARD should be considered. In case of exposure to COVID-19, hydroxychloroquine and sulfasalazine may be continued, but the panel noted uncertainty regarding temporarily stopping methotrexate or leflunomide in this situation. In case of documented or presumptive infection, ACR guidelines recommend stopping sulfasalazine, methotrexate, and leflunomide [21].

**Biologic DMARDs and targeted synthetic DMARDs**

The risk of infection observed in RA patients treated with biologic Disease-Modifying Antirheumatic Drugs (bDMARDs) is generally considered slightly higher (from 1.5- up to 2-fold) compared with conventional synthetic (csDMARDs) [43]. According to NHS, any biologic therapy puts a patient in the high-risk category for acquiring COVID-
of 1783 patients with rheumatic diseases with COVID-19 in whom were treated with infliximab and secukinumab [5]. The Global adalimumab required hospitalization. The other two patients were treated with TNF inhibitors (53.7%) and the rest with other agents. Three out of the four positive cases had RA, two were on etanercept, one was on abatacept, and one was on tofacitinib. Two were on methotrexate, one on leflunomide, and two on low-dose steroids. Only one out of these patients required admission. The DMARDs were withdrawn at symptom onset, and no significant relapses of the rheumatic disease were documented in any patient. None of the patients died or developed severe respiratory complications. This preliminary study shows that patients who received cs/b/ts DMARDs do not seem to be at an increased risk of respiratory or life-threatening complications from COVID-19 as compared with the general population [42].

Another group collected data from 530 patients treated with bDMARDs for RA (49.6%), spondyloarthropathies (36.8%), and other connective tissue disorders. Most patients were treated with TNF inhibitors (53.7%) and the rest with other bDMARDs. Only three patients in this group were recorded to have mild COVID-19 by positive swab of which only one patient with sarcoidosis who had been treated with adalimumab required hospitalization. The other two patients were treated with infliximab and secukinumab [5]. The Global Rheumatology Alliance Global Registry data shows that out of 1783 patients with rheumatic diseases with COVID-19 infection, 30.7% patients were on biologic DMARDs [4]. In the C19-GRA data, treatment with b/tsDMARD monotherapy (largest subgroup being anti-TNF medications, 52%) just prior to COVID-19 diagnosis was significantly associated with a lower odds of hospitalization compared with no DMARD therapy (OR = 0.46). After controlling for sex, age over 65 years, rheumatic disease, smoking, comorbidities, csDMARD monotherapy, other b/tsDMARD monotherapy, csDMARD-b/tsDMARD combination therapy (excluding anti-TNF), NSAID use, and glucocorticoid dose, a significant inverse association between any anti-TNF therapy and hospitalization was found [17]. Evidence of high levels of cytokines like IL-6 and TNF in severe COVID-19 can explain the possible beneficial effect of anti-TNF therapy in preventing severe disease [44]. Preclinical data have even suggested the possible role of anti-TNF therapy in treatment of COVID-19 infection [45]. However, there is currently no evidence indicating that TNF inhibition is harmful to patients in the context of COVID-19.

It is not currently known whether there is any association between rituximab and risk of infection with COVID-19. It has not been associated with significantly increased rates of infections for most rheumatologic indications. B cell depletion has been postulated to compromise antiviral immunity by impairing the development of anti-SARS-CoV-2 antibodies and increases the risk of reinfection. On the other hand, complications of COVID-19 like thromboses, severe lung pathology, and hyperinflammation bear similarity to certain rheumatological conditions like antiphospholipid syndrome, ILD, and Macrophage Activation Syndrome (MAS) for which Rituximab has been shown to be effective—thereby signaling a role for rituximab in treatment of these complications [46].

The NHS recommends either to assess whether maintenance treatment with rituximab can be reduced to 1 pulse or to consider delaying intervals between rituximab infusions [1]. The risk of infections (including serious infections) is higher in those who develop severe hypogammaglobulinemia and neutropenia or are on concomitant immunosuppressive therapy [47].

The risk of tsDMARDs is roughly comparable with bDMARDs. JAK inhibitors like baricitinib and tofacitinib and IL-6 inhibitor, tocilizumab, have been studied in COVID-19. A study identified a group of drugs which inhibit clathrin-mediated endocytosis by targeting members of numb-associated kinase (NAK) family—including AAK1 and GAK—which has shown to reduce viral infection in vitro. Baricitinib was identified as a NAK inhibitor, with high affinity for AAK1—thus helping in countering COVID infections—that too at doses used to treat RA (2-4 mg daily). Tofacitinib, however, did not show detectable inhibition of AAK1 [48]. This theory was contested by JAK-STAT blocking by Favalli et al. who stated that production of interferon, which is one of the most powerful innate immune responses to prevent viral replication, is impaired by baricitinib by blocking the JAK-STAT pathway [49]. Hence, further studies are required to confirm the efficacy of baricitinib in COVID-19, and until such time, its use in RA should be with caution. There is currently no data on other drugs approved for RA like upadacitinib or filgotinib and their association with COVID-19.

IL-6 and IL-1 play an important role in the hyper-inflammatory reaction—which is the massive release of pro-inflammatory mediators causing Cytokine Release Syndrome (CRS)—responsible for ARDS, lung injury, and multiorgan dysfunction seen in severe COVID-19 patients [50]. Hence, blockades of these two cytokines have been studied in the treatment of COVID-19. In a retrospective study of 21 patients with severe COVID-19, a single dose of 400 mg of tocilizumab improved oxygen saturation, CRP levels, CT scan abnormalities, and lymphocyte counts [45]. Tocilizumab as a therapeutic strategy may be promising, but a more reliable data in the form of a randomized controlled trial is required for definitive proof.

ACR guidelines state that patients with rheumatic diseases, in the absence of COVID-19 infection, may continue IL-6...
inhibitor therapy if available or switch to a different biologic should be considered in case of non-availability. The panel noted uncertainty regarding the use of JAK inhibitors in this situation. The panel suggested that for patients with moderate to high disease activity despite optimal conventional synthetic DMARDs, biologics may be started. In patients following COVID-19 exposure, the panel suggested that immunosuppressants, non-IL-6 biologics, and JAK inhibitors should be stopped temporarily, pending a negative test result for COVID-19 or after 2 weeks of symptom-free observation. In select circumstances, as part of a shared decision-making process, IL-6 inhibitors may be continued following COVID-19 exposure. In patients with documented COVID-19 infection, the panel suggested that non-IL-6 biologics, and JAK inhibitors should be stopped or held and that IL-6 inhibitors may be continued as a part of a shared decision-making process [21].

NICE guidelines recommend to consider switching the same biologic therapy to subcutaneous form if available. If this is not possible, alternative subcutaneous treatment can be considered [1].

**Other drugs**

NICE guidelines recommend giving denosumab, extending dosing intervals to no longer than 8 months. Treatment with zoledronic acid can be postponed for up to 6 months [1].

ACR guidelines recommend continuation or initiation of full-dose ACE inhibitors or Angiotensin Receptor Blockers (ARBs) for hypertension [21]. In fact, sudden withdrawal of Renin-Angiotensin-Aldosterone-System (RAAS) inhibitors may be harmful, and it has even been suggested that RAAS inhibitors may be beneficial in COVID-19 infection [51].

Pneumococcal and influenza vaccine is also recommended for patients when available by the Australian Rheumatology Association [52].

Vitamin D has immunity boosting and anti-inflammatory properties and has been recommended in vulnerable populations [53]. The Korean College of Rheumatology recommends spending 15 min per day under sunlight (except Systemic Lupus Erythematosus patients) for vitamin D [54].

**Resuming therapy after infection**

The ACR guidelines state that for uncomplicated infections treated in an ambulatory setting, DMARDs and biologics may be restarted within 7–14 days of symptom resolution. For asymptomatic positive patients, treatment may be restarted after 10–17 days of the positive report. Re-initiation of treatment needs to be individualized for patients recovering from severe illness [21].

**Conclusion**

The use of anti-inflammatory and immunomodulatory therapy in the setting of RA and COVID-19 is a double-edged sword. Early and appropriate use of these drugs has been shown to be beneficial in tackling the cytokine storm, but their use in an advanced stage is controversial. On the other hand, if used too early, these drugs may even promote viral replication by their immunosuppressive effects, especially corticosteroids [28]. While the few studies on patients with rheumatic diseases provide reassurance about incidence of life-threatening COVID-19 infection in immunosuppressed patients, it is imperative to understand that 90% of those patients had adopted preventive measures like social distancing, and use of masks and gloves since the beginning of the epidemic [5]. Hence, while waiting for evidence-based recommendations, preventive measures like practicing cough hygiene, regular hand washing, social distancing, and avoiding public places cannot be overemphasized. It is important to keep disease under control as that poses a considerable risk for acquiring infections. In general, a non-infected patient can be safely continued on ongoing therapy to keep the disease under control without significant increase in risk of acquiring the infection. In case of a disease flare, DMARDs and even biologics may be initiated when indicated. The decision to continue DMARDs or immunosuppressive agents including biologics and small molecules in exposed or confirmed cases should be left to the treating rheumatologist, who should do a proper risk-benefit analysis.

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Alakendu Ghosh - Conceptualization, literature review, reviewing the manuscript and supervision

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