SARAA
South African Rheumatism & Arthritis Association
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26 March 2020

To: SARAA members & affiliates

RE: ACCESSIBILITY TO CHLOROQUINE & TOCILIZUMAB FOR PATIENTS WITH RHEUMATIC CONDITIONS CHALLENGED BY A GLOBAL PANDEMIC.

Dear colleagues

There has been a tidal wave of interest in some of our rheumatologic therapies, most notably chloroquine (CQ) or hydroxychloroquine (HCQ) and tocilizumab (TCZ); both having been touted as therapies of interest in the treatment of the novel coronavirus SARS-CoV2 or COVID-19.

Despite a lack of robust evidence for their use, there is some empirical data to suggest benefit in certain subgroups of patients with COVID-19. Internationally, and more recently locally; these medicines have found their way onto national guidelines, further sparking a frenzy for access to these agents.

The potentially dire consequence of this, is an unacceptable lack of access to these well-established therapies, for our patients with rheumatic diseases.

1. Tocilizumab

In South Africa, TCZ, an IL6 inhibitor, is registered for the treatment of moderate to severe rheumatoid arthritis, polyarticular and systemic JIA. Interest in TCZ as a potential treatment for severe COVID-19, was fuelled by the recognition of elevated IL6 levels in some patients with severe respiratory complications, notably the cytokine storm associated with this infection.

Case studies and small series, along with a retrospective single-arm observational study emanating from China, have shown some benefit in clinical outcomes of severe presentations of COVID-19. Despite, a lack of robust evidence, the use of TCZ has been seen as a potentially life-saving treatment in extreme cases, of critically ill, ventilated patients with elevated CRPs or IL6 levels (where available). A randomised control trial of TCZ in COVID-19 is currently underway and hopefully will provide us with more information. There are many other potential cytokine and targeted therapies which mechanistically could be helpful in these cases, however for now, their benefits are still anecdotal.

We are aware of communications from members of other medical disciplines involved in the treatment of COVID-19, "suggesting" that rheumatologists switch patients on IL6 blockers to alternative therapies, as a way of ensuring supply for the expectant sick COVID-19 patients.

- SARAA advises rheumatologists not to alter therapy for any other reason, but for the well-being of their patient. Managing patients on biological agents is highly specialised, with nuances to selection, dosing, monitoring and switching/stopping, that can only be understood through experience.
- Roche pharmaceuticals has confirmed that there is sufficient stock for all existing rheumatic patients, as well as potential new ones where indicated. There is also sufficient subcutaneous TCZ, and rheumatologists have the option of using this preparation for their new patients, which is not an option for COVID-19 treatment. *Please find attached a letter from Roche, as well as a summary of available evidence for the use of TCZ in COVID-19.*

2. Chloroquine or hydroxychloroquine

We have seen a dramatic escalation in the prescribing and dispensing of CQ, with stockpiling in large hospital pharmacies, pre-emptively for use in COVID-19 disease. Moreover, the largest consumers of CQ derivatives are doctors themselves. This has led to a dramatic reduction in availability for our patients in need; particularly SLE patients, where it forms the backbone of therapy and where the **proven** benefits are life-saving.

The antiviral effects of CQ are well documented in-vitro; principally by its ability to effect changes in pH-dependant processes through the alkalinisation of lysosomes, impeding viral entry and replication. However, in vivo studies of influenza, dengue fever, Ebola and chikungunya virus, did not translate clinically. In vitro studies in SARS-CoV-2 suggest an additional mechanism of action, whereby CQ prevents effective virus binding to angiotensin converting enzyme 2 (ACE2), thus limiting viral entry. Although ad hoc studies from China and France have implied a role for CQ/HCQ in COVID-19, there are many unanswered questions regarding its place in the armamentarium of COVID-19 management. These studies though encouraging, were limited by study design: varied, small, underpowered with allocation bias, and no intermediate follow up data. Choice of drug compound varied between studies i.e. CQ PO4 vs HCQ (CQ SO4 was not trialled - this is the CQ product available in SA); with in vitro studies suggesting HCQ works better; and dosing regimens varied from centre to centre. Many clinical trials are underway, and we are cautious but hopeful that our "old favourite" could prove to be a "wonder-drug" for the devastating coronavirus pandemic.

At present, there is a global shortage of the active pharmacological ingredient necessary to manufacture CQ/HCQ. This is further hampered by an existing import/export ban of the base product. In South Africa; suppliers, depots, hospitals and clinics are sitting at <15% of stock availability. This implies that whatever stock exists, needs to be monitored closely, and used appropriately for registered indications, until more stock becomes available.

The shortage of CQ is not a new problem. Since the discontinuation of Nivaquine, a Sanofi product, in late June last year, we have been struggling with limited stock of this essential therapy. Up until right now, Plasmoquine (Chloroquine sulphate) was the only CQ product available in SA, and the small manufacturing company has struggled to meet demands. Hydroxychloroquine, the preferred formulation due to lesser toxicity, used in almost all other countries, is not registered in SA, and can only be attained through a section 21 application.

SARAA has been addressing this issue for many years. Discussions with Sanofi have been disappointing, citing a lack of feasibility as the reason for not registering their HCQ product, Plaquenil. This stance has remained unchanged with regards to its known indications. After years of communication with SAHPRA regarding access to HCQ, we were alarmed by a recent announcement to the medical community, which failed to acknowledge the use of CQ in the treatment of SLE and RA. We are still awaiting clarification on this. National Department of Health and state procurement committees have been helpful, recognising the significance of CQ in the armamentarium of RA & SLE treatment. Availability is somewhat better in larger state institutions, however stockpiling for COVID-19 use could present a new challenge.

Access to CQ/HCQ for COVID-19 has been actively addressed. There are discussions between Sanofi, SAHPRA and the Department of Health. Further donations are being offered by pharmaceutical companies towards the COVID-19 crisis and the WHO has also supplied medications for access via large-scale multicentre clinical trials. Austell, a local pharmaceutical company, has been given the go ahead to import 500 000 units of CQ phosphate for use in COVID-19.

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Meanwhile, SARAA will continue to address the challenge of access for our patients. Together with partnering patient organisations, we continue to drive awareness of CQ use in the treatment of SLE and RA. The pharmacy council of SA and GP groups are warned of overzealous, off-label prescribing and bulk buying of this drug. State-based rheumatology units have been encouraged to make bulk section 21 applications for HCQ for their SLE patients.

While we struggle to access CQ for our patients, we can offer some reassurance for our doctors and their patients with lupus. CQ and HCQ has a very long half-life of 40-50 days, with tissue deposition at concentrations 200-20000 times that of blood levels. This implies that its effects persist well beyond its intake. Patients on CQ/HCQ for over 6 months could endure a month, possibly 2 months off treatment without affecting their disease activity. Those on treatment for over 5-7 years should already be on reduced dose regimens of 2 to 3 days a week, to limit the very real concerns of CQ toxicity.

As rheumatologists, our ultimate responsibility is to ensure the best treatment for our patients. We are also physicians and an at-risk community of the global population, trying to deal with an ominous threat to human existence as we know it. Rheumatologists are well placed to advise on the use of these agents; and many of the other potential immunological therapies under investigation for the management of COVID-19, based on years of clinical experience. There is much room to work together with all specialities at confronting this virus, whilst not neglecting all other non-COVID patients.

Warm Regards,

Kavita Makan

President

On behalf of SARAA EXCO

SARAA ENDORSED