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FIRST EDITION

RHEUMATOLOGY IN THE TIME OF A PANDEMIC

SARAA

An official publication of the South African Rheumatism and Arthritis Association

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Reference: 1. AMGEN Fact Sheet. C2020. Accessed 25/3/2020. Available from https://www.amgen.com/about/quick-facts/ **2.** AMGEN Our Strategy. C2017. Accessed 6/4/2020. Available from https://www.theamgendifference.com/our-strategy.html

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Romilda Bozzetti is a digital artist from Italy who enjoys working in a cubist-type style. Cubism aims to represent the fusion of the past and the present as well as simultaneous, multiple-perspective views of the subject.
We were inspired to use this cubist perspective to illustrate NewsRheum, to portray the duplicity in our patients with rheumatic diseases; who at first glance may be seen to have physical disabilities or deformities, but who demonstrate beauty and positivity despite their ailment.

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Rheumatology in the time of a pandemic

Message from the President

Rheumatology in the time of a pandemic

John Lennon said: "Life is what happens to you while you're busy making other plans." These words become more and more significant for me each year. Sitting with the team of Ann Lake Publications in early January, conceptualising this publication, I was ill-prepared for the impact of the avalanche ahead of us. COVID-19 may have taken over 2020, but in so doing, it has awakened the scientific community, it has shattered social standards and placed compassion, collaboration and consideration for humanity ahead of all else.

NewsRheum follows a long hiatus for an official publication for SARAA. This first edition, will echo in the start of what I hope to be a lasting endeavour for SARAA, one that allows local clinicians and academics an opportunity to share knowledge and experience. Regular features will include: Lest we forget, a contemplation of seminal articles in history, Enter the rheum clinic, which will focus on clinical aspects of rheumatology and, Rheum with a view, a pictorial view of cases in rheumatology. We will also have a community page, Rheum Lites, focusing on what is happening in rheumatology in SA and regularly include CPD accredited content.

Inspired by the works of afflicted artists such as Rubens and Klee, and recognising beauty in the abnormal, NewsRheum celebrates the art of rheumatology. Each edition will feature an original artwork on the cover to symbolise the strong connection between rheumatology and art.

As president of SARAA, I would like to thank all contributors to this publication, particularly in light of our circumstances. My hope, looking beyond this pandemic, is that the positivity and comradery which we as a society have shown through this difficult time, strengthens our society, and allows SARAA to stand tall among medical associations.

Dr Kavita Makan, SARAA President
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Editorial

The COVID-19 pandemic has not only caught our attention, but is having profound effects on medical practice as a whole; and rheumatology has not been spared. A large part of the usual activity of rheumatology units has been absorbed by the growing need to manage patients with COVID-19. Many people will die due to the pandemic, and others may have worse outcomes from their chronic disease, due to lack of access to their physicians and diversion of hospital resources to treat the seriously ill infected by COVID-19. Patients are reluctant to do face-to-face consultations because of being fearful to contract coronavirus. Telemedicine is to gaining momentum across the world, and while it all looks straightforward, there are many ethical and legal considerations. Dr Etheredge tackles the ethical issues of navigating the 'new normal". The impact of the corona virus pandemic will be felt in decades to come. The economic effects will have huge implications on the survival of the population at large. The article, "Psychological effects of Covid-19 now and beyond" highlights possible contributors and considerations as a treating physician, in relation to the patient as well as the treating doctor.

Contrary to initial widespread concerns about use of immunosuppressive therapy in Covid-19, it is now recognised that therapeutic cytokine inhibition might in fact be useful in the hyperinflammatory state of Covid-19. A lot has been written about steroids since the beginning of the pandemic. While there was acknowledgement that it might be useful in the treatment of Covid-19, people were "being careful not to forget" the dark side of steroid treatment. Lest we forget, reminds us where we come from with steroids. Currently, steroids form part of the treatment of Covid-19 for a selected group of patients, and has reduced mortality. We must be grateful to Kendall and Hench for their brave efforts. It is important to have a wide differential diagnosis when evaluating Covid-19 patients, especially acute presentations. The case of Bechet's disease covered in this journal clearly illustrates the overlap often encountered in patients with rheumatic diseases and Covid-19.

It has not been all doom and gloom in the rheumatology community as it was early in the pandemic. A concern was that patients with rheumatic disease who are immunosuppressed were at high risk of infection and death. A study in the USA demonstrated that patients with rheumatic disease and Covid-19 infection were more likely to require mechanical ventilation but had similar clinical features and hospitalisation rates as those without rheumatic disease. To date, there is no data to suggest that patients with rheumatic diseases are at increased risk of COVID-19. The concern is that, with the widespread use of antirheumatic drugs in patients with COVID-19 in areas affected by the pandemic, drug supplies of patients with rheumatic diseases may be endangered.

Lessons learnt during this pandemic should make us stronger and better. It is important to make a virtue of necessity by unlocking a new era in patient management.

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Lest we forget

The story of cortisone in the treatment of rheumatoid arthritis

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"If I have seen further it is by standing on the shoulders of Giants"
- Isaac Newton

Rheumatology is one of youngest subspecialties of internal medicine. It is arguably one of the fastest growing clinical disciplines in the 21st century. That patients with rheumatic diseases today are enjoying a better health related quality of life is no small part the result of decades of close collaboration between astute clinicians. and scientists working in the areas of molecular medicine, chemistry, and immunology. Incremental improvements in clinical outcomes for chronic, potentially debilitating and disabling diseases like rheumatoid arthritis (RA) are due to a combination of advances in bedside diagnosis and assessment, coupled with smarter use of traditional antirheumatic agents and development of novel targeted biologic agents.

The objective of this series of articles is to remind us of the outstanding discoveries in both the basic and clinical sciences that have shaped current practices in rheumatology. The amazing story of the discovery of cortisone and use in the treatment of rheumatoid arthritis stands out for many reasons. Cortisone was the first drug to produce profound improvement in inflammatory arthritis. Importantly its discovery and subsequent use in clinical medicine underscores the importance of collaboration between basic scientists and clinicians. So here is the story...

The setting was the Mayo Clinic, Rochester, Minnesota with two central researchers, Eric Calvin Kendall, PhD, and Philip Showalter Hench, MD, and patient Mrs 'G'. Kendall was an outstanding scientist who in 1914 at the age of 28 was the first biochemist to crystallise thyroxin from almost three tons of hog thyroid tissue![1] Hench was an astute clinician and first Chief of Rheumatology at the Mayo Clinic.

In the 1930s Kendall had redirected his research interests to the highly competitive area of isolating hormones of the adrenal gland. After two false claims of having found the hormone, 'cortin', he isolated six adrenal compounds, which he labelled compounds A-F, of which he considered compound E most likely to be 'cortin'. Working in a small laboratory in Switzerland, the Polish biochemist, Tadeus Reichstein, had at about the same time identified the same hormone, which he called compound Fa.[2] Whilst Kendall enjoyed little research support initially, things changed during World War II when rumours that cortin enabled German Luftwaffe to fly at high altitude. In response to this apparent threat, the US government prioritised funding for cortin research. Additionally, Kendall was able to secure a weekly supply of 400kg adrenal glands from the pharmaceutical company, Parke-Davis, for whom he worked simultaneously to extract adrenaline.[2]

The process of extracting compound E proved to be laborious with a low yield but things changed when a young scientist, Lewis Sarett, working for Merck on the cortin project, joined Kendall on a three months sabbatical. In 1944 Sarett succeeded in synthesising compound E from ox bile, a complex process that required 38 steps! The next hurdle was to find a clinical indication for the of use cortin as the military's interest had waned by this time. Thus, cortin, for which Merck had spent over $13 million in development, had become 'a treatment in search of a disease'.[3]

At about the same time Hench observed that inflammatory arthritis in an elderly doctor improved spontaneously with onset of jaundice. He subsequently published a series of papers in which he noted that a correlation between severity of jaundice and improvement in joint inflammation.[4] Administration of bile salts, human and ox bile failed to make a difference to joint inflammation, but he observed some benefit after artificial induction of jaundice. He found a similar effect of pregnancy on inflammatory arthritis which lead him to postulate that an unknown substance "X" was produced by these conditions. Having befriended Kendall earlier, he and Kendall surmised that substance 'X' and cortin were one and the same humoral factor. They decided to test cortin in rheumatoid arthritis but finding a suitable patient was the next challenge...

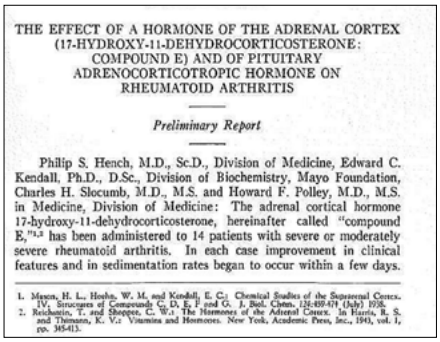
In the summer of 1948, a 29-year-old woman, Mrs 'G', from Indiana came to the Mayo Clinic determined not leave until her rheumatoid arthritis was cured. Kendall and Hench having procured 5g of compound E from Merck, got Charles Slocumb, MD, a junior rheumatologist working with Hench, to administer Mrs 'G' with the first intramuscular dose of 50mg on September 21. She showed remarkable improvement within days of receiving twice daily injections of compound E. From being bed bound she was now able to visit other patients and go shopping. According her medical notes her joints has improved at least "50%".

Initially Hench kept his observations under wraps, but at the insistence of Merck he invited a handful of senior physicians a few months later to witness the response to compound E in two other patients. To the astonishment of the

visiting physicians, the patients showed a similar dramatic improvement. Within six months of treating Mrs 'G', Kendall and Hench presented their findings in 14 patients to a packed audience at the weekly Mayo staff meeting. The seminal publication appeared a few months later in the Proceedings of the Mayo Clinic **(Figure 1)**.[5] Compound E was renamed 'cortisone' by Kendall and Hench and was soon to be touted as a miracle cure. With various pharma companies clamouring to produce the drug, Kendall gave his patent rights to the Mayo Clinic and each company was to pay royalties to the Research Corporation of New York. With advances in manufacturing techniques, cortisone was more readily available by the mid-1950s. As for Kendall and Hench, they together with Reichstein, were awarded the Nobel Prize for Physiology and Medicine "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects[6] **(Figure 2)** - a mere two years after Mrs 'G' received the first dose of cortisone. Hench, in appreciation of the work of his colleagues at the Mayo, shared his prize money with Charles Slocumb, Howard Polley and Mary Pantaleon, his ward nurse.

Mrs 'G' was sadly less fortunate - within a month of starting cortisone she became cushingoid and having mood swings and psychosis later, resulting in her being transferred to a psychiatric ward. Despite a reduction in the cortisone dose, she remained unwell and required blood transfusions for anaemia. After discharge being from the Mayo, she refused to take cortisone and died in 1954. The cause of death was not clear, but according to the former Chief of Rheumatology at the Mayo, Dr Eric Matteson at a recent American College of Rheumatology annual meeting, Mrs 'G' probably succumbed to a gastric haemorrhage.[3]

Thus, the early excitement for cortisone was soon to be replaced by scepticism and fear as more patients suffered complications of high dose cortisone. Further negative publicity was to come when in 1954 a British study found cortisone and ACTH therapy were no better than aspirin in early rheumatoid arthritis.[7] Hench



THE EFFECT OF A HORMONE OF THE ADRENAL CORTEX (17-HYDROXY-11-DEHYDROCORTICOSTERONE: COMPOUND E) AND OF PITUITARY ADRENOCORTICOTROPIC HORMONE ON RHEUMATOID ARTHRITIS

Preliminary Report

Philip S. Hench, M.D., Sc.D., Division of Medicine, Edward C. Kendall, Ph.D., D.Sc., Division of Biochemistry, Mayo Foundation, Charles H. Slocumb, M.D., M.S. and Howard F. Polley, M.D., M.S. in Medicine, Division of Medicine: The adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone, hereinafter called "compound E,"[1,2] has been administered to 14 patients with severe or moderately severe rheumatoid arthritis. In each case improvement in clinical features and in sedimentation rates began to occur within a few days.

1. Mason, H. L., Hoehn, W. M., and Kendall, E. C.: Chemical Studies of the Suprarenal Cortex. IV. Structures of Compounds G, D, E, F, and G. J. Biol. Chem., 126:839-878 (July) 1938.
2. Reichstein, T., and Shoppee, C. W.: The Hormones of the Adrenal Cortex. In Harris, R. S., and Thimann, K. V.: Vitamins and Hormones. New York, Academic Press, Inc., 1943, vol. 1, pp. 345-413.

Figure 1. Seminal paper on the effect of cortisone on rheumatoid arthritis.[5]

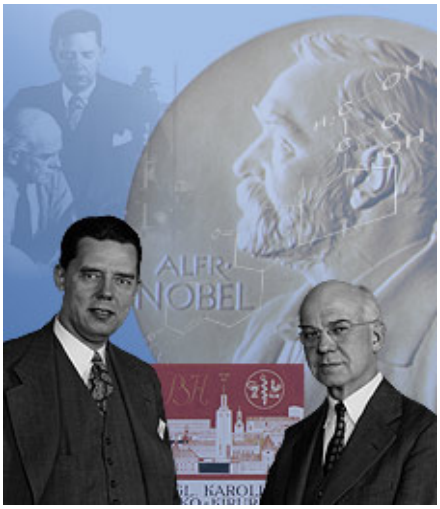


Figure 2. Philip S Hench (left) and Edward C Kendall (right) joint 1950 Nobel Prize winners for Physiology and Medicine with Tadeus Reichstein (not shown)

was not convinced by these findings and he felt betrayed when a larger study by the Empire Rheumatism Council again showed similar negative outcomes.[8] That a later study with the more potent corticosteroid with less mineralocorticoid effects, prednisolone, showed superiority over aspirin[9] made little difference to Hench's sense of betrayal towards his British and American peers.[2] His growing disillusionment led him take early retirement in 1957 after which his health declined. He died from pneumonia in 1965 at the age of 69. Kendall was forced to retire in 1951 when he turned 65 but continued to work for another 20 years at Princeton University and after a short illness died at the ripe old age of 86 in 1972.

The tortuous and bumpy road to the discovery and clinical application of corticosteroids in clinical practice in many ways reads like a Shakespearean tragedy. But beyond the emotional and physical rollercoaster ride that both researchers and patients experienced, the discovery of cortisone raises many ethical and scientific questions in the context of 21st century clinical practice. Would this kind of human experimentation with a new pharmaceutical agent, in the absence of efficacy and safety studies in animals, be allowed today? Given that initial randomised control studies with parent compound, cortisone, failed to show superiority over aspirin, coupled with horrendous side effects of the drug, how likely is it that pharma in today's economic environment would pursue further drug development as was the case with cortisone? What would be the fate of the millions of patients who have benefitted from corticosteroid therapy for a variety of clinical indications outside of the rheumatic diseases? Finally, in the context of the current Covid 19 pandemic, might we have been deprived of having a drug like dexamethasone that is showing so much promise in the treatment of Covid pneumonia?[10]

References

1. Kendall EC. Reminiscences on the Isolation of Thyroxine. Mayo Clin Proc. 1964;39:548-52.
2. Burns CM. The History of Cortisone Discovery and Development. Rheum Dis Clin North Am. 2016;42(1):1-14.
3. Collins TR. The Tortured Path to the Cortisone Discovery Atlanta: American College of Rheumatology; 2019 [Available from: https://www.the-rheumatologist.org/article/the-tortured-path-tothe-cortisone-discovery/.
4. Hench PS. Effect of Jaundice on Rheumatoid Arthritis. Br Med J. 1938;2(4050):394-8.
5. Hench PS, Kendall EC, et al. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin. 1949;24(8):181-97.
6. Nobelprize.org. The Nobel Prize in physiology or medicine 1950.: Nobel Media AB 2020; 2020 [Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1950/.
7. A COMPARISON of cortisone and aspirin in the treatment of early cases of rheumatoid arthritis; a report by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, A.C.T.H., and Other Therapeutic Measures in Chronic Rheumatic Diseases. Br Med J. 1954;1(4873):1223-7.
8. EMPIRE Rheumatism Council; multi-centre controlled trial comparing cortisone acetate and acetyl salicylic acid in the long-term treatment of rheumatoid arthritis; results up to one year. Ann Rheum Dis. 1955;14(4):353-70.
9. A COMPARISON of prednisolone with aspirin on other analgesics in the treatment of rheumatold rthritis. Ann Rheum Dis. 1959;18:173-88.
10. Horby P, Lim WS, Emberson J, Mafham M, Bell J, Linsell L, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv. 2020:2020.06.22.20137273.

Ethics and COVID-19 - maximising remote consultation for doctors and patients

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COVID-19 has also compelled us to reconfigure our ethical thinking. As cases edge towards their peak, we have seen country after country adopt a 'public health ethics' framework out of necessity, as supply of hospital beds simply cannot match demand.

COVID-19 has drastically changed our world, in ways that I think we would have been hard-pressed to imagine even six months ago. Across the international healthcare arena, the virus has created an environment of fear and panic, which is acutely felt by both health professionals and patients. For health professionals, the practical manifestations of this fear can be seen in higher levels of absenteeism and an understandable unwillingness to work in 'under resourced' environments; especially where availability of personal protective equipment (PPE) is limited. For patients, the sense of fear and uncertainty has resulted in a lack of health-seeking behaviour, and a demonstrable unwillingness to visit doctors' rooms or other health facilities.

A lot of the time, such behaviour is desirable. Decreased footfall through practitioners' rooms and hospitals means fewer vectors for COVID. However, fear-driven, health-averse behaviour that has detrimental effects on patient outcomes and overall quality of life is worrying. Some classic examples involve surgical patients postponing doctors' visits, where ultimately the condition becomes critical and emergency surgery is required. Delaying management under these circumstances can negatively affect the patient's prognosis and patients need to be made aware of this.

A paradigm shift – changing our ethical thinking

COVID-19 has also compelled us to reconfigure our ethical thinking. As cases edge towards their peak, we have seen country after country adopt a 'public health ethics' framework out of necessity, as supply of hospital beds simply cannot match demand. The main difference between public health ethics and "modern bioethics" is their stance towards patient centeredness. Modern bioethics, which is anchored by the principle of autonomy, promotes patient-centred care as its zenith. Public health ethics promotes the welfare of society or a collective over that of the individual. Whilst modern bioethics facilitates the notion of "customer as king" (or patient as king in this context), public health ethics provides compelling justification for triaging a very elderly COVID-19 patient with extensive comorbidities to palliative care, and directing active management towards someone with a better prognosis (even if the elderly patient had requested maximum intervention – as is his or her autonomous prerogative).

In the current framework of fear and health-averse behaviour, one of the main challenges facing clinicians and ethicists is how to ensure that current patients (i.e. those who have an established relationship with the clinician, whom the clinician has been treating for some time) still receive appropriate care and follow-up with as much risk minimisation as possible. We are obliged to explore avenues of care provision that facilitate minimum personal contact with patients. This not only reduces transmission risk, but also spares the patient that anxiety which is a natural by-product of seeking healthcare during this pandemic.

Adapt to survive

In disciplines geared towards management of chronic cases like rheumatology, geriatrics, neurology, endocrinology and others, an excellent ally in managing current patients from a safe distance is the digital consultation. In cases where a physical examination is not required, consultation on a digital platform can, and should, suffice as the primary interaction between clinician and patient. Perhaps this is only for "the time being". But its possible that

this is the new normal, and if COVID-19 is with us for some years to come, we must adapt to survive.

Although this sounds relatively straightforward, in practice digital medicine and telehealth have enjoyed only sluggish uptake in South Africa, which may be explained by the following real or perceived limitations:

- Concerns about differential access to telehealth, where patients who have good connectivity, bandwidth and funds to purchase data are more likely to benefit
- The inability to perform a physical examination on a virtual platform,
- Uncertainty about the legal implications of utilising telehealth
- Uncertainty about remuneration for private practitioners
- Logistical complications associated with choosing the most appropriate telemedicine consultation platform
- Bandwidth, data and streaming constraints

However, telehealth is widely used internationally. In South Africa, I would propose that we consider COVID-19 as an opportunity to streamline our consultation processes and provide value-based care. Moreover, digital consultations in the current healthcare context can significantly advance the best interests of our patients.

Whilst the risk mitigation aspects of telemedicine consultations during COVID-19 are hardly disputable, there are still numerous practical considerations that can seem daunting for first time telemedicine users – both patient and clinicians alike. The remainder of this article makes recommendations which, I hope, will clarify some of the ethical and legal grey areas and facilitate wider telemedicine uptake across the spectrum.

What telemedicine software should I use?

When choosing a platform for digital consulting, remembering 'what not to do' – and working backwards from there – can be a helpful place to start. The Health Professions Council of South Africa (HPCSA) has published Guidelines on Telemedicine, and these have been updated to facilitate access to telehealth during COVID-19. One of the most important pitfalls to avoid is consultation over "social media". This includes consulting on public fora like Twitter and Facebook. However, WhatsApp is also considered social media, and as such we need to proceed with maximum caution if we choose this as a consulting platform.

Using software like Zoom and Skype for telemedicine consults is acceptable, but remember that these platforms are not necessarily compliant with the Protection of Personal Information Act (POPIA).

Using software like Zoom and Skype for telemedicine consults is acceptable, but remember that these platforms are not necessarily compliant with the Protection of Personal Information Act (POPIA). This is another area where many health professionals come a-cropper. For example, Zoom for Telehealth offers a paid digital consulting platform that is HIPAA compliant. However, HIPAA and POPIA are quite different pieces of legislation, and we must not to assume that legislation applicable in other countries is passable in South Africa.

To enhance POPIA compliance in telehealth, South African practitioners should be especially cautious regarding information storage, access, retrieval and subsequent processing. Some practical tips involve storing digital recordings on POPIA compliant platforms, password protecting stored data and familiarising ourselves with the terms and conditions associated with each storage option.

Given these imitations of social medical platforms and freely available software, the best options for telehealth consults are likely those provided by medical schemes or made available to practitioners by private hospital groups. Unfortunately, these might not be accessible to those consulting with state-based patients, foregrounding another ethical issue which it is beyond the scope of this paper to discuss. And once again, third-party digital platforms and not without their limitations.

What are our obligations for record-keeping in digital consultations?

As in physical consultations, clinical notes and observations resulting from telehealth interactions should be recorded in the patient file. In the digital realm, an easy way to bolster our clinical record-keeping is to record the interaction using the functionality that is often built-in to the telehealth platform. It is important to notify patients that you are recording the consult for the purposes of record keeping. Furthermore, its vital to remember that the patient may also record the consultation should they choose to. The upshot of this is that we always need to maintain exemplary professionalism. And this is an area where practitioners sometimes let their guard down, as physical distance between us and the patient in the digital realm can lead to a false sense of security and over-confidence.

Who can we consult with on a telehealth platform?

Until COVID-19 changed our health system, and the world, the HPCSA recommended that practitioners only use digital platforms to consult with existing patients. This meant that a consult with a new patient had to

be in person. These guidelines have been amended, and now allow digital consults with new patients, provided these are in the "best interests" of the patient.[8] Evaluating what constitutes the best interests of a patient you have never met before can be a tricky business, so it's always better to err on the side of caution. If you are unsure about the appropriateness of a digital consult, it is perfectly reasonable to advise a face-to face appointment. This does not mean that information (such as patient history) cannot first be exchanged during a telehealth appointment. However, new patients are unknown entities, and we may not be able to reliably evaluate their best interests without seeing them in person.

Consent to telehealth consulting

When consulting on a telehealth platform, it's important that we don't fall into the trap of taking things like consent or confidentiality "for granted" (as one doctor told me she did on a recent radio interview). This is especially important when it comes to telehealth consults with existing patients, with whom we already have a relationship. Whichever telemedicine platform you choose to utilise, its important to be aware that the different consulting format most likely requires some adjustment to the consent process, whether a new or existing patient. Over and above the standard information shared as part of informed consent, communicating the following points to patients in advance of a telemedicine consult will serve to strengthen the consent process:

- Whether or not you are recording the consultation for patient records
- The fact that no digital platform is entirely safe, and there is always the chance (though it is likely small) that a consultation could be hacked
- That the patient is responsible for ensuring the safety of their device with up-to-date antivirus, firewall and other necessary protections (and reassure the patient that you have taken the same precautions)
- That if you have any doubt about the utility of an online consult to benefit the patient, you will recommend a physical exam
- That costs associated with bandwidth, device usage and data on the patient's device will be for the account of the patient
- [If in the private sector] How much the telehealth consult will cost, and whether the bill will be submitted to medical aid, or the patient will be required to transfer cash and claim back from medical aid. Here it is important to remind the patient that medical aid may not cover the full cost of the consult.
- If consulting over a third party telehealth platform, such as one sponsored by a hospital group or medical scheme, make the patient aware that there may be additional terms and conditions imposed by that organisation, which they should familiarise themselves with.

Signing out

For most of us, living with the uncertainty that COVID-19 has brought into our lives is a depressing business, and it looks like dark days ahead. During these times, I'd argue that we can best fulfil our obligations to our patients (and ourselves) by keeping our distance and keeping everyone as safe as we can. COVID-19 has not brought with it a plethora of new opportunities. However, the option of telemedicine as the 'new normal' is surely one of them, and one we could all benefit from embracing.

References

1. Ranney ML, Griffeth V, Jha AK. Critical supply shortages—the need for ventilators and personal protective equipment during the Covid-19 pandemic. NEJM. 2020 Apr 30; 382(18): e41. https://www.nejm.org/doi/full/10.1056/NEJMp2006141
2. Rosenbaum L. The untold toll—the pandemic's effects on patients without Covid-19. NEJM. 2020; 382:2368-2371. https://www.nejm.org/doi/full/10.1056/NEJMms2009984
3. Wallis CJ et al. Risks from deferring treatment for genitourinary cancers: A collaborative review to aid triage and management during the COVID-19 pandemic. European Urology. 2020; 78(1): 29-42. https://doi.org/10.1016/j.eururo.2020.04.063
4. Mahomed, S. Ethics and Public Health: A South African Perspective. In Nortjé N, De Jongh J and Hoffmann WA (Eds). African Perspectives on Ethics for Healthcare Professionals. 2018. Springer.
5. Rosenbaum L. Facing covid-19 in Italy—ethics, logistics, and therapeutics on the epidemic's front line. NEJM. 2020. Online edition: https://www.nejm.org/doi/full/10.1056/NEJMp2005492.
6. Grobler C, Dhai A. Social media in the healthcare context: Ethical challenges and recommendations. S Afr J Bioethics Law 2016;9(1):22-25. https://doi.org/10.7196/SAJBL.2016.v9i1.464
7. Bouter C, Venter B, Etheredge H. Guidelines for the use of WhatsApp groups in clinical settings in South Africa: medicine and the law-in practice. SAMJ. 2020; 110(5): 364-8. http://www.samj.org.za/index.php/samj/article/view/12929/9243.
8. Health Professions Council of South Africa. Notice to amend Telemedicine Guidelines during COVID-19 – dated 3 April 2020 | HPCSA E-Bulletin. https://www.saheart.org/cms/content/104-notice-to-amend-telemedicine-guidelines-during-covid-19-%E2%80%93-dated-3-april-2020-%7C-hpcsa-e-bulletin
9. Health Professions Council of South Africa. Ethical guidelines on social media. 2019. https://www.hpcsa.co.za/Uploads/Events/Conference/20Aug_Session_4_Guidelines_for_Social_Media.pdf
10. Government of the Republic of South Africa. Protection of Personal Information Act No. 4 of 2013. https://www.gov.za/sites/default/files/gcis_document/201409/3706726-11act4of2013protectionofpersonalinforcorrect.pdf

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Introducing the adalimumab biosimilar[4]

AMGEVITA™ (adalimumab)

Amgevita™

- is approved across all key adalimumab indications[5]
- has similar safety, efficacy and immunogenicity as the originator biologic[6,7,8,9]

References: 1. AMGEN Therapeutic Area Heritage. C2019. Accessed 25/3/2020. Available from https://www.amgenbiosimilars.com/heritage/therapeutic-area-heritage/ **2.** AMGEN Fact Sheet. C2020. Accessed 25/3/2020. Available from https://www.amgen.com/about/quick-facts/ **3.** AMGEN Biotech. C2017. Accessed 25/3/2020. Available from https://www.amgenbiotech.com/manufacturing-innovation.html **4.** Kozlowski S. US FDA perspectives on biosimilar biological products. c2014. Accessed 25/3/2020. Biotechnology Technology Summit. IBBR University of Maryland, Rockville, MD. Available from https://www.ibbr.umd.edu/sites/default/files/public_page/Kozlowski%20-%20Biomanufacturing%20Summit.pdf **5.** AMGEVITA™ package insert. 18 Feb. 2020. **6.** Kaur P, Chow V, Zhang N, *et al.* A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab. *Ann Rheum Dis* 2017;76:526-533. **7.** Cohen S, Genovese MC, Choy E, *et al.* Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: a randomised, double-blind, phase III equivalence study. *Ann Rheum Dis* 2017;76:1679-1687. **8.** Cohen S, Pablos JL, Pavelka K, *et al.* An open-label extension study to demonstrate long-term safety and efficacy of ABP 501 in patients with rheumatoid arthritis. *Arth Res & Ther* 2019;21:84. **9.** Papp K, Bachelez H, Costanzo A, *et al.* Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicentre, phase III study. *J Am Acad Dermatol* 2017;76:1093-1102.

S4 **AMGEVITA** 40 mg solution for injection in pre-filled syringe. Each single dose pre-filled syringe contains 40 mg of adalimumab in 0.8 ml (50 mg/ml) solution. Reg. No. 51/30.1/0678. S4 **AMGEVITA** 40 mg solution for injection in pre-filled pen. Each single dose pre-filled pen contains 40 mg of adalimumab in 0.8 ml (50 mg/ml) solution. Reg. No. 51/30.1/0678. For full prescribing information refer to the package insert approved by the medicines regulatory authority.

Amgen South Africa (Pty) Ltd., Co. Reg. No.: 2011/112148/07. Building D, Ballyoaks Office Park, 35 Ballyclare Drive, Bryanston Ext. 7, 2021. Tel: 011 100 5300 Fax: 011 100 5301. Adverse Event Reporting email safety-south-africa@amgen.com. Expiry Date: April 2022. PR-AMV-ZAF-000018.

AMGEN® 40 YEARS

Rheum with a view

Blending in with Behçet's

Dr Pramone Moodley
Dr Kavita Makan
Chris Hani Baragwanath Academic Hospital and University of the Witwatersrand

Case Study

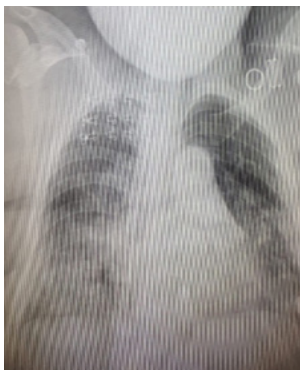


Figure 1.

Figure 2.

In April 2020, Ms. E.L, a 62-year-old black African female with Behçet's disease (BD), known to the rheumatology unit at Chris Hani Baragwanath Hospital in Soweto, presented to the medical acute care unit with acute onset of respiratory symptoms. The patient was diagnosed with BD in 2001, with early presentations including oral ulcers, uveitis, arthritis and colitis. The patient was previously treated with Azathioprine and Methotrexate, however on her current admission had been off immunosuppressive therapy for many years. She had well controlled hypertension on three agents, as well as human immunodeficiency virus (HIV) with a CD4 count of 495 cells/uL, on first line antiretroviral treatment. The patient had been admitted previously for flares of colitis in 2005 and 2007, however since then her BD was in remission. There was no documentation of previous lung involvement in association with her autoimmune disease, and no previous episodes of tuberculosis or other opportunistic infections. She was unemployed, a non-smoker and of sober habits.

Ms. E.L's presenting symptoms involved a one week history of shortness of breath, dry cough (no haemoptysis) with pleuritic chest pain, and associated febrile episodes. There was no history of headaches, ulcers, arthralgias, abnormal bowel movements or abdominal pain. On examination she was noted to be normotensive with a blood pressure of 113/79 mmHg, pulse rate of 110 beats per minute, a temperature of 39˚C and an oxygen saturation of 77% on room air, which improved to 94% on a rebreather mask. She was notably in respiratory distress, with bilateral crackles on auscultation. Cardiovascular exam revealed no features of heart failure or pulmonary hypertension. There were no mucocutaneous lesions suggestive of BD, abdominal and neurological examination was normal and there was no evidence of deep vein thrombosis. The patient was started on antibiotics as well as oral paracetamol, and prophylactic Clexane.

A chest x-ray revealed diffuse lung parenchymal opacities, notably involving the lower zones and the electrocardiogram showed a sinus tachycardia with no other abnormalities. Admission blood work revealed a white cell count of $10.32x10^9$/L, and a haemoglobin of 13.3 g/dl. Notably, the CRP, ESR (Erythrocyte sedimentation rate), D-Dimer and activated partial thromboplastin time (aPTT) were raised at 103 ug/mL, 98 mm/hr, 0.71mg/L and 50.7 seconds respectively. The acute onset of respiratory symptoms prompted testing for SARS-CoV-2 by reverse transcriptase polymerase chain reaction testing (RT-PCR) on a nasopharyngeal swab specimen, which was positive for the coronavirus. The patient eventually required mechanical ventilation due to persistent hypoxaemia, and an increased effort of breathing. Intravenous hydrocortisone was added to treatment. Unfortunately, the patient demised a few hours later due to ventilator-related complications, a mere 36 hours into her admission.

Discussion

The novel coronavirus disease of 2019 (COVID-19) is currently a global pandemic, with 138 134 active cases and 2456 deaths in South Africa as of 28 June 2020.[1] It has created many diagnostic and therapeutic challenges; and for rheumatologists in particular, the pulmonary and systemic features can mimic disease presentations of many systemic rheumatic diseases.

Behçet's disease (BD) is a chronic inflammatory disorder characterized by multisystemic vasculitis. The disease which is prevalent in Turkey, the Middle East and Asia, is rarely seen in Sub-Saharan Africa, where higher mortality and nervous system disturbances are more frequently documented.[2,5] Common presentations include mucosal lesions (oral and/or genital ulcers), skin lesions in the form of papulopustular lesions and erythema nodosum, and uveitis.[2,3] Other organ manifestations include arthritis, thrombosis (more venous then arterial), neurological, pulmonary and gastrointestinal manifestations.[2]

Pulmonary manifestations in BD

Pulmonary involvement occurs in up to 10% of patients.[2] The most common findings in the lung include pulmonary vascular disorders such as pulmonary artery aneurysm(PAA), pulmonary artery thrombosis (PAT), pulmonary infarct with associated pulmonary hemorrhage and involvement of small-sized vessels.[6] These manifestations arise from vasculitis and/or the occlusion of pulmonary vessels.[2] Recurrent pneumonia, bronchiolitis obliterans organised pneumonia, and pleurisy are some of the other findings seen.[7] Pulmonary vasculitis can be considered as either microscopic or macroscopic (PAA ,PAT). Both entities present with similar symptoms such as dyspnoea, cough and chest pain ,however

haemoptysis is more commonly seen in the setting of PAA as noted in a case series of 47 patients with PAA studied by Seyahi et al.[6] Pulmonary artery involvement is related to significant morbidity and mortality.[4]

Chest Xray findings include rounded opacities, hilar fullness and mass lesions which represent pulmonary PAA.[2,7] Parenchymal changes involving atelectasis, wedge shaped, or linear shadows, ill defined, nodular or ground glass opacities may arise and are generally associated with pulmonary haemorrhage and/or infarcts. Commonly, PAA are identified in the right lower lobar arteries, followed by the right and left main pulmonary arteries.[7] Our patient was found to have bilateral lower zone opacities which may be in keeping with PAA or PAT however this seems unlikely in the context of dry cough without haemoptysis. A retrospective study of 44 patients with BD found up to 31.2% with normal chest X-rays had evidence of pulmonary or vascular changes on computed tomography (CT) scan. Interestingly, patients with haemoptysis and underlying PAT may present with normal X-rays reiterating the importance of CT scan, namely CT pulmonary angiogram.[2] CT scan imaging may help elucidate changes in the vessel wall or lumen, aneurysms with fusiform or saccular swellings, thrombus with associated filling defects. Evaluation of the heart chambers may reveal thrombus (especially right ventricle) which frequently accompanies PAA.[2] Parenchymal involvement on CT may present as ill-defined nodular opacities, sub-pleural alveolar infiltrates and focal atelectasis with or without cavitation.[2] Collateral vessel formation due to chronic thromboembolism may also be noted.

Pulmonary manifestations in COVID-19

Sixty-nine percent of patients with COVID-19 will present with an abnormal chest X-ray, with the number reaching 80% during the course of admission.[9] Findings include bilateral, peripheral mainly lower zone opacities, with consolidation, similar to those presenting in the patient reported. Ground glass opacities are a less common feature. Pleural effusions seen rarely.[9,10] Notably,the chest X-ray may be normal early in the disease in ambulatory patients.[11] Computed tomography (CT) has been found to be more useful in detecting earlier COVID-19, thereby eliminating other diagnoses.[12] Abnormalities observed include ground glass opacities, consolidation and interlobular septal thickening most commonly in the lower lobes.[13]

Thrombosis

Thrombosis is also a major feature of both diseases. This is an image of another patient, with severe hyperinflammatory syndrome due to COVID-19. Digital ischemia is a known clinical presentation of systemic vasculitis (primary or secondary). In the context of COVID-19, it has been documented as a manifestation of hypercoagulability, a prominent finding in the pandemic. BD commonly presents with vasculitis involving the arterial or venous systems[14] with venous thrombosis seen in up to 20% of patients.[3,15] Thrombosis seen in BD is largely due to vascular damage associated with endothelial dysfunction with elevated nitric oxide and homocysteine levels, increased thrombin formation and decreased fibrinolysis.[16] Similarly, COVID-19 is associated with increased clotting due to endothelial injury and an elevated level of prothrombotic factors[17] in association with coagulation abnormalities.[18,19,20] Both diseases may manifest with venous thrombosis in the form of deep vein thrombosis (most commonly);[14,17] however, dural sinus thrombosis and Budd-Chiari syndrome are seen more in BD.[14,17] Arterial complications seen in COVID-19 include strokes and acute limb ischaemia with carotid, pulmonary, iliac and femoral thrombosis seen predominantly in BD.[14,17]

Treatment

Distinguishing between these two disease entities is paramount in ensuring correct therapeutic choices. Treatment modalities for BD lung and thrombotic manifestations include high dose glucocorticoid therapy, traditional immunosuppressive agents such as cyclophosphamide or azathioprine, and more recently tumour necrosis factor inhibitors (TNFis).[3] Anticoagulation has a definite role in the treatment of venous thrombosis, however long-term anticoagulation is controversial in the context of thrombosis with co-existing PAA owing to risk of life-threatening bleeding.[22] COVID-19 pneumonia might be responsive to similar immunomodulatory therapies, with recent results of the RECOVERY trial showing potential benefit with Decadron. Furthermore, anticoagulation appears to be an essential part of the COVID-19 treatment paradigm.[17]

Conclusion

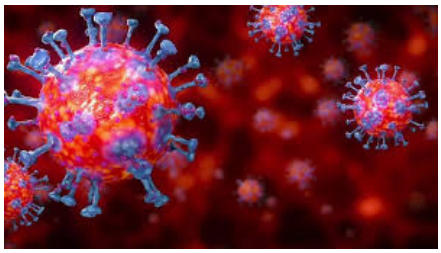
Although the diagnosis of COVID-19 can be easily confirmed with PCR testing, false negatives do occur, and it is imperative in the current climate of COVID-19 to consider the complexity of distinguishing between systemic manifestations of rheumatic diseases like BD and COVID-19 disease presentations.

RheumQUIZ

Questions

1. What are some of the extra-pulmonary manifestations of COVID-19?
2. In COVID-19 hyperinflammatory syndromes, which two classes of cytokine inhibitors have been trialed for use?
3. What is the pulmonary manifestation of Behçet's disease most commonly associated with mortality?

For answers to these questions, please see page 26.



The psychological effects of COVID-19 – now and beyond

Mr Gerhard I Grundling
Clinical Psychologist: Benoni
Director: Clinical Psychology Forum of SA

Many adults and children alike around the world most probably will recognise the picture above of the SARS-COV-2. What is vastly different from seeing the virus in such an objective way, is the experience of the pandemic of the virus that plays out in unique ways on individual, family, social and within larger community systems.

What do we know about disasters and more specifically the COVID-19 pandemic and its psychological effects on homo sapiens? We need to learn from present experiences, impact, and research to be better equipped and prepared in future to deal with these large-scale disasters.

This millennium has seen the emergence of coronavirus culminating in the severe-acute-respiratory-syndrome (SARS) and COVID-19 having an enormous impact on the world population. On January 30, 2020, the World Health Organisation declared COVID-19 an international public health emergency.[1]

The nature of COVID-19 is such that it is highly infectious. Being a virus, people cannot identify this 'enemy' which makes people feel uncertain and generate a sense of being out of control. Clustering these two factors together give rise to anxiety and fear.[2]

Psychological effects Macro-level interventions

When considering COVID-19 on a macro-level, various interrelated systems contribute to the psychological effects. How these systems interact and communicate can determine the level of psychological impact and to what extent people will experience it as negative. The following figure gives a good overview of the interplay between these systems. It is an intricate psychosocial relationship between COVID-19, government and the rules of managing the spread of the disease, the information supplied and also the quality of the information, the population and the healthcare provider that stands central and is required to stabilise or create equilibrium to mitigate the impact on the patient.[3]

from the Vrije Universiteit Brussel, specialising in health and primary care psychology as well as resilience, wrote an article that was published by the World Economic Forum, stating that lockdown is the world's biggest psychological experiment. Prof van Hoof, as clinical psychologist and her team of researchers, indicated that the consequence of lockdown will bear a high price in both the short- and long-term. The price will primarily be in triggering mental health problems that will give rise to concomitant physical symptoms and possibly worsening of existing chronic conditions.[4]

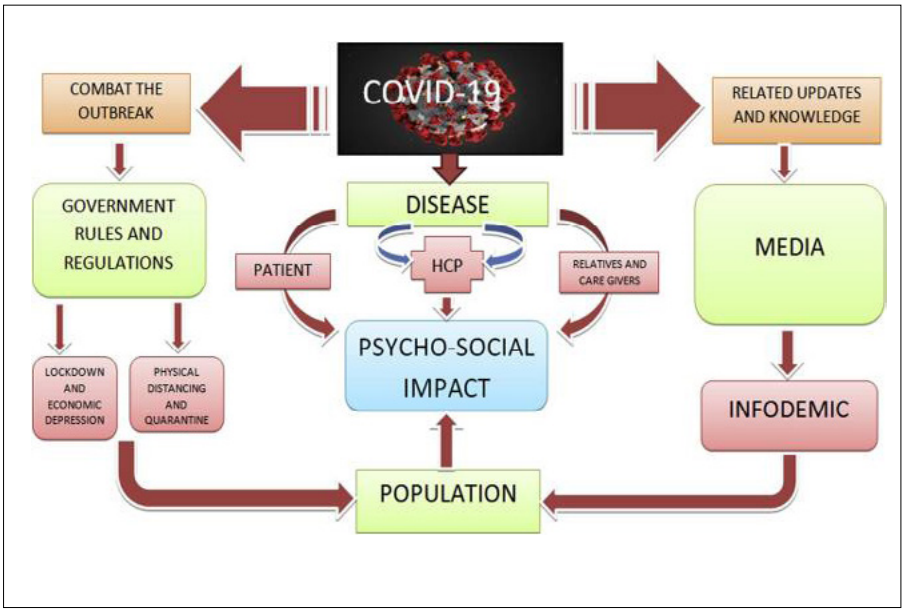


Figure 1. From: Dubey S et al; Psychosocial impact of COVID-19; Elsevier Public Health Emergency Collection – Diabetes Metabl Syndr, 27 May 2020, electr publ.

Lockdown and quarantine

Contributing to the psychological impact is the social isolation that started in China and then spread to many countries around the world. Billions of people have been restricted from daily activities. This has been a concern for psychologists worldwide, although necessary, this has had many psychological ramifications. Professor Elke van Hoof,

In March 2020, the Lancet published a review of 24 studies[5] that investigated the psychological effects of quarantine on people who have been exposed to a contagious/infectious disease. Two psychological factors stand out as occurring very commonly: Irritability and low mood. Other symptomatology observed were emotional exhaustion, confusion, post traumatic symptoms, depression,

anxiety, stress, insomnia, and anger. Stressors identified were infection fears, longer quarantine duration, boredom, frustration, inadequate supplies, inadequate information, financial loss, and stigma. Substance abuse was also identified as a factor that presented after the quarantine period ended. Health workers consistently reported higher levels of symptoms and had a statistically significant greater chance of developing post traumatic symptoms; and their recovery time took longer.

Thus, health workers are at greater risk for negative psychological impact. The occurrence of these negative psychological effects does not mean that lockdown or quarantine is not necessary, but rather that when taking people's freedom away, it must be carefully considered and if at all possible other measures such as social distancing would be preferable.

Media, flow of information and COVID-19

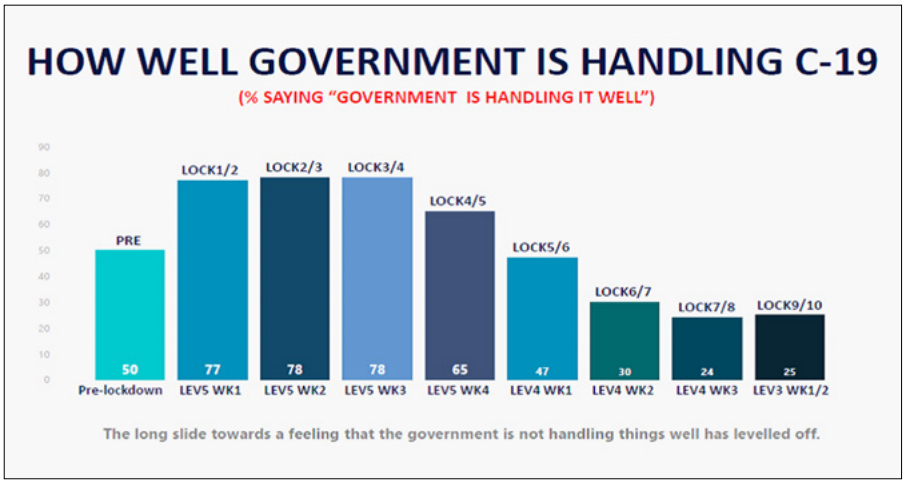
Both the flow of information and the quality of such can have a beneficial impact and/or a negative impact. Social media especially can spread disinformation and become part of the process of creating greater levels of anxiety. This was seen very soon after the start of the COVID-19 pandemic in China. The level of disinformation was such that it started a wave of panic, anxiety, stigmatisation, and avoidance behaviour on a large scale. The spread of this was imminently faster that the spread of the COVID-19. This has led to the director-general of the World Health Organisation to coin the term "coronavirus-infodemic". There was a clear indication that various groups and individuals took advantage of the COVID-19 pandemic and started to use it to their own benefit to generate income through the spread of disinformation. Early on in the pandemic this reached such levels that it started to be identified as health crime due to the adverse impact on people, such as generating negative sentiments about certain groups that has the potential to develop into adverse reactions, for example the isolation of others, racism, etc. Further research is needed to be able to identify approaches that can be used to ensure the flow of correct and helpful information. In this regard healthcare providers have been identified as a trusted source by the public to ensure the transfer of information, factually.[6,7]

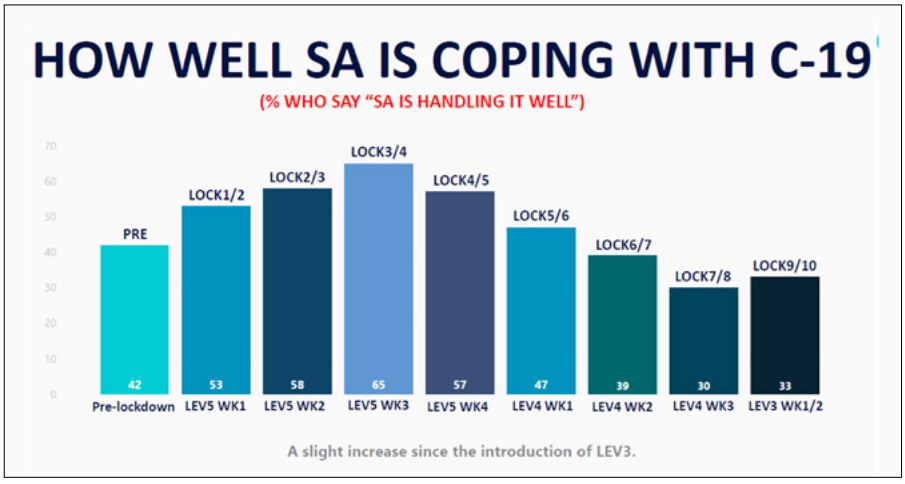
The South African scenario

COVID-19 has been fast spreading and anxiety and distress has widely been observed. These psychological effects and responses are to be expected and are normal responses, as such it is part of adapting to the continuous changing situation. How this is managed is important because when resilience is low this will result in the psychological impact to become pathological. It is helpful to assess the impact of COVID-19 closer to home and see how South Africans have experienced and responded to the pandemic. All Told, a market research company, has done regular weekly updates on the South African population.

South Africans have both in terms of their perception of how government is handling COVID-19 and how they personally are handling COVID-19 responded with more negative views. There is a levelling off since the start of lockdown level 3, but it remains low. This means that the general mood about the pandemic has deteriorated over time.

There are especially high levels of anxiety about financial matters, price increases, mental health, and lawlessness present with South Africans. South Africans have a pessimistic view of the short to medium term future saying things will get worse before it will improve. Being extremely worried and fearful is present amongst 15 to 20 % of South Africans. Interestingly many more South Africans are more concerned about impending mass deaths due to COVID-19 than their own death. All figures are from the start to week 10 of lockdown.[8]





Figures 2 and 3. Source: All Told, SACOVID-19, Chart Report for round 9, 15 June 2020.

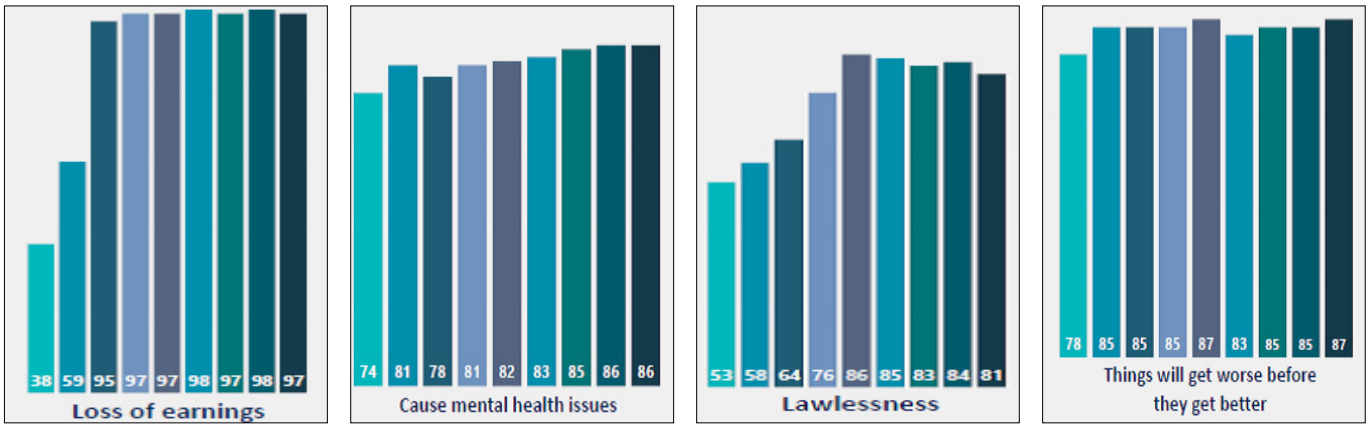


Figure 4a,b,c and d. Source: All Told, SACOVID-19, Chart Report for round 9, 15 June 2020.

The majority of South Africans are still anxious and worried about COVID-19. During week 1 of lockdown 81% of South Africans were worried but since week 6 of lockdown, this has stabilised between 55% – 60% of South Africans being fearful of COVID-19. This is quite a high percentage, and this could have a longer-term negative impact on mental health. Most South Africans will only visit their doctor if it is essential – approximately two thirds, and one third will visit their doctor as the need arises.[8]

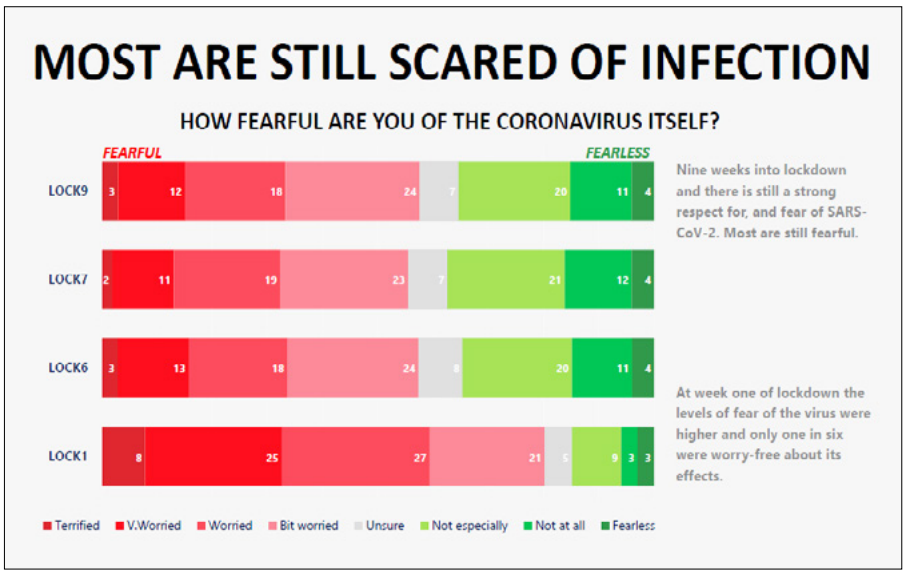


Figure 5. Source: All Told, SACOVID-19, Chart Report for round 9, 15 June 2020.

At-risk groups

People with mental health disorders

People with mental health disorders are at higher risk for infectious diseases such as COVID-19. Their health outcomes are poorer for both physical ailments as well as psychological disorders. Contributing to this are lowered awareness, impaired risk perception, decreased personal care and at times reduced concern about personal hygiene. The COVID-19 pandemic may contribute to the worsening of symptoms such as increased anxiety levels, lower mood, more compulsive and obsessive symptoms (increased hand washing, etc). Incorrect assumptions about body sensations and interpreting these as COVID-19 symptoms can occur and lead to overburdening of healthcare services.[9]

Old age

The fact that older people are more at risk for COVID-19 infection and the higher mortality rate amongst older people give rise to higher levels of concern and anxiety. With age comes a decline in the ability to manage one's life and stress. Increased isolation, cognitive decline and an increase in chronic physical conditions make this group in society more vulnerable and they need special care. Physical activity and social interaction and support are necessary to ensure a higher level of resilience towards the COVID-19 pandemic.[10]

Children

Children are in a continuous process of development on various levels. The COVID-19 pandemic has had a direct impact on their developmental trajectories due to being isolated from their peers, school closures, heightened levels of fear and anxiety at home and even being exposed to violence during these stressful times. Children are at higher risk and therefore more vulnerable and demand closer attention to their general wellbeing to ensure a more favourable transition of the pandemic period. The expectation that the pandemic is going to be present for quite some time make this more challenging to ensure that long-term negative impact on development and mental health can be managed appropriately.[11]

Healthcare providers

Previous research and the present pandemic indicate that healthcare providers have a higher risk to experience negative psychological effects from COVID-19 than the public at large. Being in the frontline they are pressurised to fulfil the expectations of the public, patients, and governments.

Working long hours under difficult circumstances and being deprived of spending time with significant others create a lack of support which is important in such uncertain times. Fear of infection and undesirable treatment outcomes of patients become mentally draining. Psychological disorders that is seen with healthcare providers are burnout, depression, anxiety, post-traumatic stress disorder and substance abuse. High levels of uncertainty, guilt and a sense of worthlessness are factors contributing to the deterioration of resilience and mental health in this group.[12,13]

COVID-19 and rheumatoid arthritis

Literature[14] indicates that up to 70% of Rheumatoid Arthritis patients experience anxiety and up to 62% can be diagnosed with depression. As with other people suffering from anxiety and depression and having a higher risk of decreased resilience and deterioration of mental health, the same is true for people afflicted by rheumatoid arthritis. There is a bilateral relationship between rheumatoid arthritis, anxiety, and depression. Depression and anxiety have the potential to impact on rheumatoid arthritis and the inverse is also true. Greater care should be taken with these patients and it is advisable to screen for symptoms that may indicate the presence of depression and anxiety.

Kaleb Michaud and his research team from the University of Nebraska Medical Centre reported in a recently completed study that the following factors were identified to have impacted patients with rheumatic disease during the COVID-19 pandemic namely heightened negative emotional experience and response to COVID-19. This was worsened by a disruption in accessing medication for their rheumatic condition, changing perceptions regarding immunosuppressive medication risks, and concerns about protective measures to mitigate COVID-19 infection. Changes in personal healthcare included cancelling of appointments and changing prescribed medication without consulting their medical practitioner.[15]

Conclusion and the road ahead

The volume of research regarding the psychological effects of the pandemic since the outbreak of COVID-19 is enormous. Coupled with research in the field of trauma and the impact of disasters as well as previous research about the psychological effects of SARS; there is much to learn. Well-designed approaches to the management of large-scale disasters as COVID-19 must be operationalised. This is a complex matter because such approaches must integrate the various societal strata in its operational management.

Psychological effects of COVID-19 are varied and widespread. The psychological impact is seen with those infected with COVID-19 and those that are not. On a macro level focus need to be on carefully choosing what interventions are needed and to have a balanced approach towards the mental health of the population. Critical is to ensure that factual and re-assuring information needs to reach the population via established media channels.

The healthcare provider must be aware of not only caring for the patient's mental health but also their own. Being resilient, means to stay connected to managing one's life mindfully, in the present moment, and to focus on ways to generate a sense of self-control. Healthcare providers must be vigilant and willing to refer patients for necessary mental health care, if indicated.

France is one of the pioneers in dealing with disasters where there is clear indication of threat to life, such as terrorist attacks, through a structured and science-based approach. The French developed an approach to the aftermath of disasters called CUMPS. Besides establishing a medical field hospital, a psychological field unit often referred to as the 'second tent' is established. This is named CUMPS – Cellule d'Urgence Médico-Psychologique. This is to give attention to the invisible psychological wounds of trauma and to act as a triage post ensuring that victims receive adequate care. This can be established in the field, at a hospital, reception area, community centres or where needed.

There is clear evidence that this active approach to managing the psychological impact of disasters is beneficial and reduce health costs in the short and long term. The visibility of support and the availability of psychological help are mediators for psychological stabilisation.[16]

References

1. WHO Website: Coronavirus disease 2019/ Events as they happen
2. Torales J et al; The outbreak of COVID-19 coronavirus and its impact on global mental health; International Journal of Social Psychiatry; 31 March 2020, V66(4), 317-320
3. Dubey S et al; Psychosocial impact of COVID-19; Elsevier Public Health Emergency Collection – Diabetes Metabolic Syndrome; 27 May 2020, electr publ
4. Van Hoof E; Lockdown is the world's biggest psychological experiment – and we will pay the price; The World Economic Forum COVID action platform; 9 April 2020
5. Brooks SK et al; The psychological impact of quarantine and how to reduce it: rapid review of the evidence; The Lancet; 14 March 2020, V395, Issue 10227, 912-920
6. Merchant RM et al; Social media and emergency preparedness in response to novel coronavirus; JAMA; 23 March 2020, V323(20), 2011-2012
7. Zarocostas J; How to fight an infodemic; The Lancet; 29 February 2020, V395, Issue 10225, 676
8. All Told, SACOVID-19, Chart Report for round 9, 15 June 2020
9. Asmundson GJG et al; How health anxiety influences responses to viral outbreaks like COVID-19: what all decision-makers, health authorities and health care professionals need to know; Journal of Anxiety Disorders; April 2020, V71, Issue 102211
10. Doraiswamy S et al; Older people and epidemics: a call for empathy; Age Ageing, 27 April 2020, V49(3), 493
11. Ghosh R et al; Impact of COVID-19 on children: special focus on psychosocial aspects; Minerva Pedriatrica, May 2020, 72(3), doi:10.23736
12. Chen Q et al; Mental Health Care for medical staff in China during the COVID-19 outbreak; Lancet Psychiatry, April 2020, V7(4), 15-16
13. Wong TW et al; The psychological impact of severe acute respiratory syndrome outbreak on healthcare workers in emergency departments and how they cope; European Journal of Emergency Medicine; 2005, V12, 13-18
14. Michaud K et al; Experiences of Patients with Rheumatic Disease in the United States during early Days of the COVID-19 Pandemic; Rheumatology (ACR), June 2020, 2(6), 335-343
15. Ziarko M et al; Mental health and Rheumatoid Arthritis: Toward Understanding the Emotional Status of People with Chronic Disease; BioMed Research International; V2019, Article ID 1473925
16. Guichet unique d'information et De declaration pour les victims: http:governement.fr/guide-victimes/en-cellules-d-urgence-medico-psychologique-cump

Rheumatological diseases affecting the hands

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The hands are a common source of pain and discomfort and may present as an isolated complaint or part of a more generalised pain syndrome. Many rheumatic diseases affect the hands and a careful examination could provide many clues to an underlying systemic disease. The approach provided in this paper will be based on the clinical components of inspection, palpation and movement and will evaluate anatomical, physiological and functional components of the hand. The clinical features are a result of disorders in the muscles, tendons, ligaments, joints, blood vessels or nerves. The abnormalities found are usually due to rheumatic diseases, but in some cases may be the consequence of primary problems with the nerves or the blood supply.

The systematic examination of the hands is aimed at evaluating the full extent of the hands and usually includes examination of the wrists. Most rheumatologists begin at the distal interphalangeal (DIP) joint and work their way proximally towards the wrist. The dorsal and the ventral surfaces of the hand need to be examined separately. Several abnormalities may be obvious, but subtle changes can only be determined by careful palpation and movement in conjunction with the inspection.

This review will provide patterns of hand involvement indicative of underlying disease. It will cover the most common diseases encountered in rheumatology clinics, but it is not exhaustive. The examples shown will span a wide spectrum of common musculoskeletal conditions illustrated by pictures, where possible. Remember that you only see what you look for!

Figure 1. A patient with osteo arthritis showing the presence of Heberden's nodes, trying to demonstrate full function of the hands.

Osteoarthritis (OA)

Osteoarthritis (OA) is a degenerative joint disease and the commonest cause of arthritis in people over the age of 50 years. The hands are commonly involved, affecting the distal interphalangeal joint (DIPJ), proximal interphalangeal joint (PIPJ) and the first carpometacarpal joint (CMCJ) at the thumb. The presence of these bony swellings at the DIPJ are called Heberden's nodes and at the PIPJ they are referred to as Bouchard's nodes. They are typically non-painful and rarely interfere with hand function, except in severe, erosive OA. These are shown in **Figure 1**.

Rheumatoid Arthritis (RA)

Hand involvement is extremely common in rheumatoid arthritis (RA) and several severe deformities may result if the disease is not treated early with disease modifying anti rheumatic drugs (DMARD) **(Figure 2)**. The common deformities of ulnar deviation and swan-neck deformity are rarely encountered nowadays, due to effective treatments being used earlier **(Figure 3)**. Early features are soft-tissue swelling around the PIPJ and metacarpo-phalangeal joints (MCPJ) **(Figure 4)**. These joints can also be palpated for tenderness. The number of swollen and tender joints in the hands (twenty) contribute towards making the clinical diagnosis and are also important in calculating inflammatory activity of the RA. Additional early features in the hands include palmar erythema and flexor tenosynovitis. The patient may show inability to complete a fist, resulting in poor grip. Subcutaneous nodules in the hands are uncommon and usually seen in patients taking methotrexate.

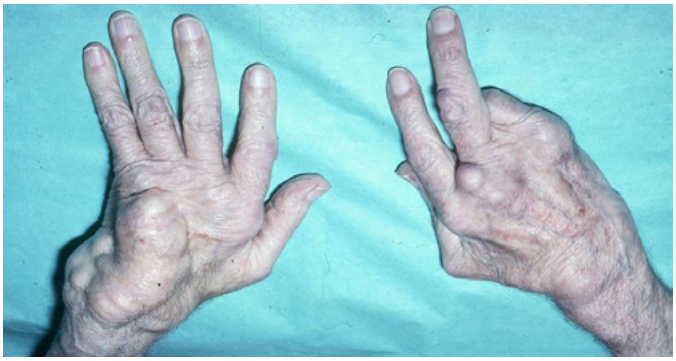

Figure 2. The severe destructive and deforming consequences of longstanding, untreated RA, showing tendon rupture, extensive dorsal tenosynovitis and ulnar deviation.

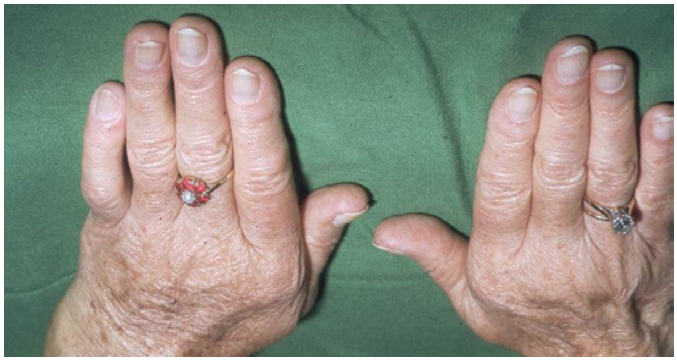

Figure 3. A patient with rheumatoid arthritis (RA) demonstrating swelling at the MCP joints and early ulnar deviation as well as synovitis of the wrists.

Figure 4. Several examples of soft-tissue swelling around the PIP and MCP joints in patients with early RA. The x-ray shows that even in patients with apparently mild disease, erosions and joint space narrowing may be seen early.

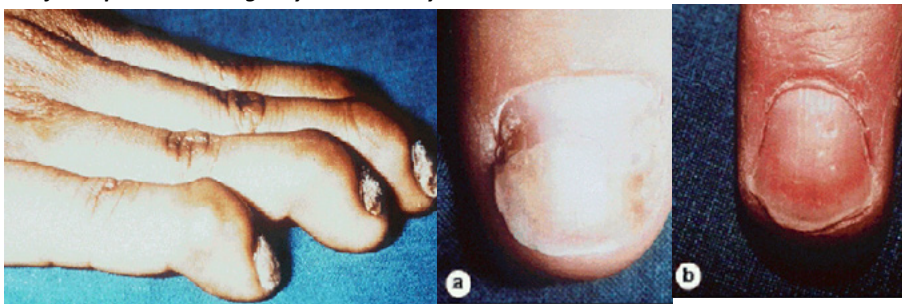

Figure 5. A patient with psoriatic arthritis (PsA), showing nail changes and "swan-neck" deformities. Also shown are other examples of nail changes in psoriasis patients.

Psoriatic arthritis (PsA)

Psoriasis is a common skin disorder which may affect the joints in approximately 15-40%, resulting in psoriatic arthritis (PsA). The hands are very commonly affected in PsA and often correlate with the extent of nail changes **(Figure 5)**. The distribution of joint involvement may overlap with that of OA and RA, but a distinctive feature of PsA is the presence of dactylitis **(Figure 6)**.

Health workers need to be aware that PsA could mimic any other form of arthritis and the diagnosis is often missed. Delayed diagnosis and late institution of treatment results in arthritis mutilans, which is characterised by shortening of digits and resorption of bone that is seen on x-ray **(Figure7)**. The distribution of joint involvement in PsA is often asymmetrical and DIPJ involvement is common. The dactylitis, nail changes and DIPJ involvement are important distinguishing features from RA The disability resulting from PsA in the hands can be as severe as that seen in longstanding untreated RA **(Figure 8)**. Differential diagnoses should also include gout and OA **(Figure 8)**.

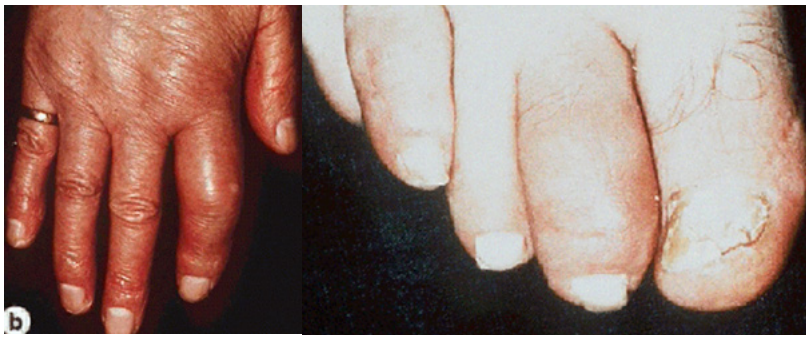

Figure 6. Dactylitis of the fingers and toes in two different patients with PsA.

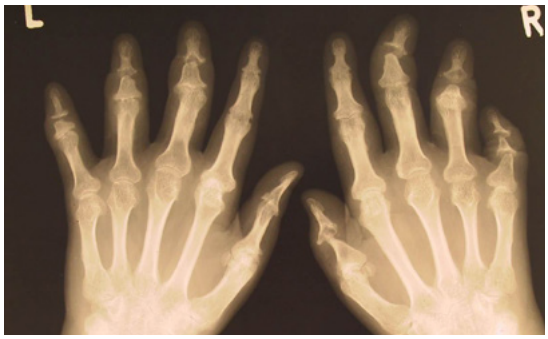

Figure 7. Radiological features of arthritis mutilans in a patient with long-standing, severe PsA.

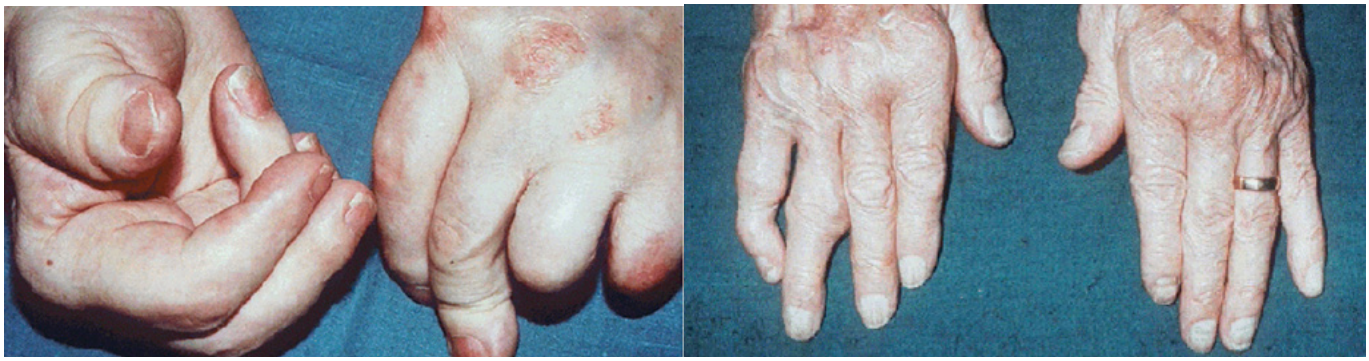

Figure 8. Examples of deformities in patients with PsA, showing changes that may sometimes be confused for RA or OA.

Gout

"When in doubt... think of GOUT!!". This is an important adage, because many health care workers forget that gout can severely affect the hands. The deposition of tophi around the PIPJ and MCPJ could result in deformities that are similar to those seen in RA **(Figure 9)**. Sometimes the tophus may look like an abscess about to rupture, causing the untrained emergency doctor to consider incision and drainage **(Figure 10)**. This should be avoided at all costs in patients with gout. The tophi often deposit along tendon sheaths and may be mistaken for rheumatoid subcutaneous nodules **(Figure 11)**. In rare instances, an isolated tophus on the DIPJ may be mistaken as osteophytes due to OA **(Figure 12)**.

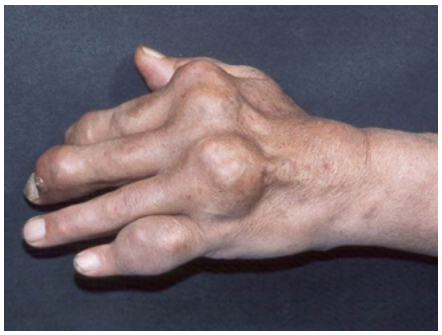

Figure 9. A patient with chronic tophaceous gout showing tophi at the MCP, PIP and DIP joints This picture also shows that gout can be a cause of "swan-neck" deformities, which are not specific for RA.

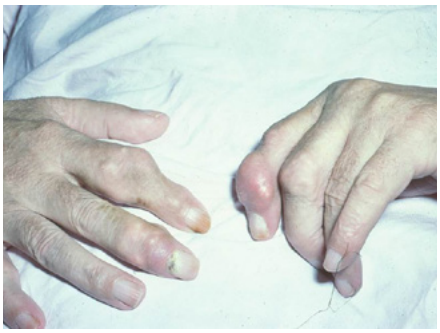

Figure 10. Another patient with chronic tophaceous gout. The urate deposition could be mistaken for an abscess by the untrained eye.

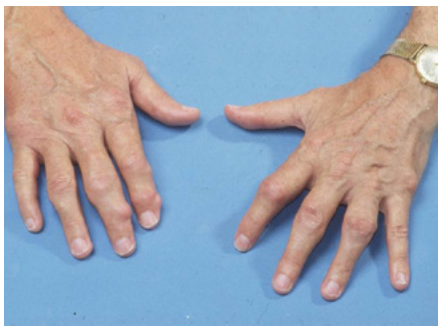

Figure 11. Gouty tophi on the fingers which could be mistaken for subcutaneous nodules due to RA.

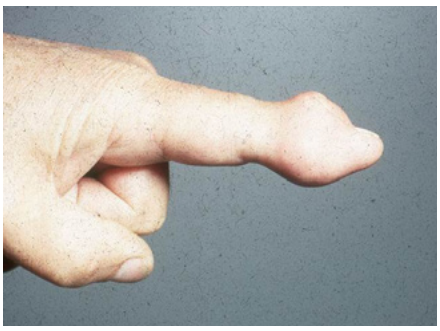

Figure 12. A gouty tophus at the DIP joint of one finger which could be misdiagnosed as OA.

Systemic sclerosis (SSc)

The hand is an extremely valuable tool in the diagnosis of limited cutaneous systemic sclerosis (lcSSc) as well as diffuse cutaneous systemic sclerosis (dcSSc). The disease is characterised by skin thickening and subsequent tightening, often leading to deformities and severe hand disability **(Figure 13)**. Careful examination of the palms will reveal tightness and the presence of telegiectatic pads on the palmar surface. There is loss of pulp at the finger tips. Early in the disease, the hands may be puffy and appear diffusely swollen **(Figure 14)**. In some patients there may be healed digital infarcts, suggestive of small vessel ischaemia and severe Raynaud's phenomenon **(Figure 15)**. Calcinosis around the joints may resemble gouty tophi, but these are clearly visible as peri-articular calcifications in the soft tissue on x-ray **(Figure 16)**.

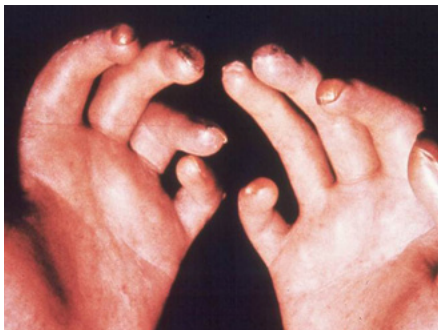

Figure 13. The hands of a patients with dcSSc, showing hand deformities due to tightening of the skin. This picture also demonstrates the telangiectatic pads which are typical of scleroderma.

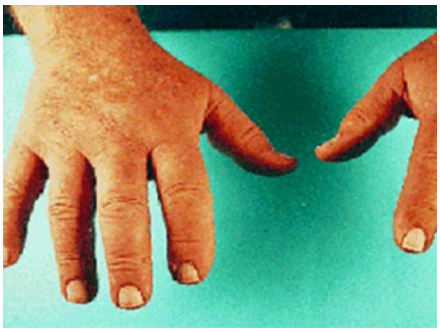

Figure 14. The puffy hands of a patient in the early stages of scleroderma.

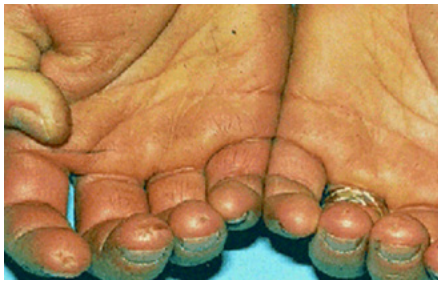

Figure 15. Digital pits in a patient with scleroderma resulting from digital infarcts that have healed.

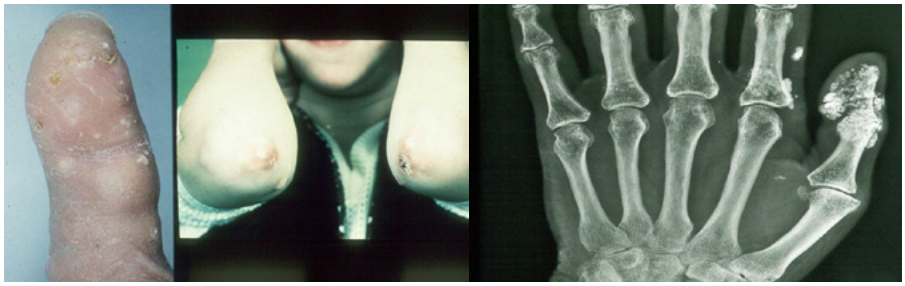

Figure 16. Calcinosis of the hands and elbows in a patient with CREST (calcinosis, Raynaud's, oesophageal dysmotility, sclerodactyly, telengiectasia) syndrome. The x-ray shows the calcification in the subcutaneous tissues.

Raynaud's phenomenon

Raynaud's phenomenon is common in young females and may be the presenting feature of an underlying auto-immune disease such as SSc **(Figure 17)**. It may be primary (unknown cause), in which case it is usually referred to as Raynaud's disease. On the other hand, it is more commonly due to an underlying systemic, auto-immune disease like SSc, systemic lupus erythematosus (SLE) or dermatomyositis, among others, when it is referred to as Raynaud's phenomenon. Positive serology usually suggests secondary Raynaud's but is not specific for any disease. In the patient with isolated Raynaud's phenomenon, examination of the nailfold capillaries using an ophthalmoscope or dermatoscope (nailfold capillaroscopy) may reveal abnormal capillaries **(Figure 18),** which could point to a specific diagnosis such as SSc, bearing in mind that certainty of diagnosis is based on the presence of classification criteria for disease.

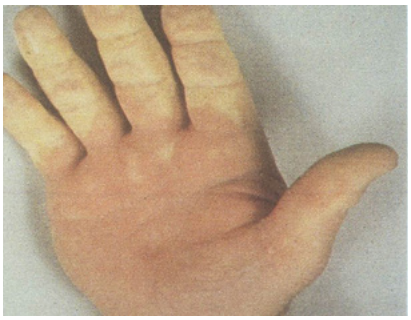

Figure 17. An example of Raynaud's phenomenon.

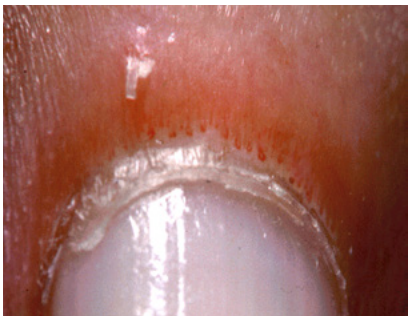

Figure 18. Nailfold capillary abnormalities in a patient with scleroderma. These are more easily seen with an ophthalmoscope or a dermatoscope.

Dermatomyositis

Dermatomyositis is an inflammatory muscle disease characterised by proximal muscle weakness and skin rashes. The rash on the hands is refereed to as Gottron's papules and usually occur over the knuckles **(Figure 20)**. They are characteristically erythematous and usually do not pain or itch. They often correlate with the extent of muscle disease, but they may also be seen in the absence of muscle inflammation (amyopathic dermatomyositis). The rash usually responds to prednisone, but in some instances, chloroquine may be an effective additional agent.

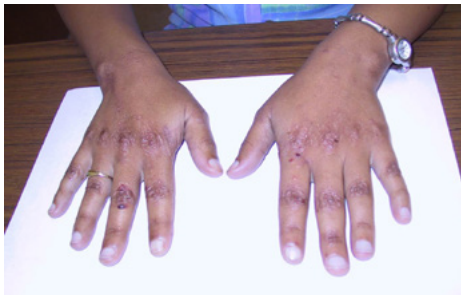

Figure 20. Gottron's papules in a patient with dermatomyositis.

Systemic lupus erythematosus (SLE)

Involvement of the hand joints is common in systemic lupus erythematosus (SLE) and is sometimes indistinguishable from that of RA. The arthritis of SLE is also known as Jaccoud arthritis, named after the man who first described the arthritis of rheumatic fever. Clinically, it manifests with mild, correctible ulnar deviation of the fingers and subluxation of the MCPJs **(Figure 19)**. It is generally regarded as a non-deforming and non-erosive arthritis. Discoid skin lesions typical of SLE may also be seen on the palmar and dorsal aspects of the hands. These are occasionally misdiagnosed as "vasculitis", but they are benign forms of discoid lupus and respond well to chloroquine treatment without immunosuppression.

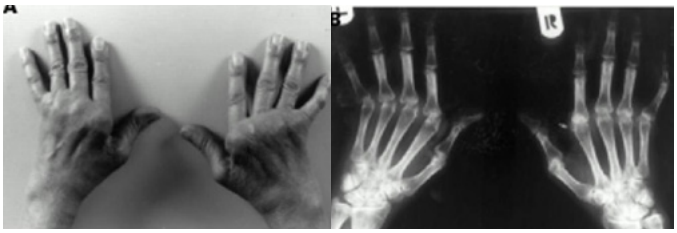

Figure 19. The arthritis of SLE, called Jaccoud Arthritis and demonstrating the ulnar deviation and subluxation at the MCP joints. The x-ray shows that in spite of these deformities, there are no erosions, as is typical of the arthritis of SLE.

Infarction and gangrene

Ischaemia to the fingers may be seen in a number of systemic diseases including hypertension and diabetes, where it is usually the result of atherosclerosis and vessel obstruction. Several auto-immune diseases can cause digital ischaemia and this is a consequence of different mechanisms. Broadly, ischaemia could result from obstruction due to changes within the lumen (hypercoaguable states), changes in the wall (vasculitis) or changes outside the wall (ischaemic contractures). In SLE, patients may experience arterial and venous thrombosis due to the anti-phospholipid antibody (APA). Some of the patients will have livedo reticularis of the limbs **(Figure 21)**, which is a clue to the diagnosis of anti-phospholipid syndrome (APS). Vasculitis may be associated with antibodies such as anti-neutrophil cytoplasmic antibody (ANCA) or other inflammatory vascular conditions. Severe swelling of soft-tissues in tight areas could lead to vascular compression from outside the vessel.

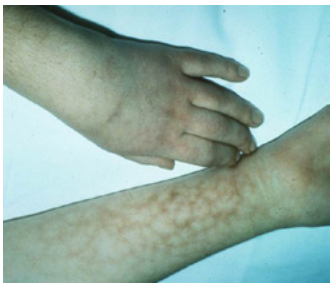

Figure 21. Livedo reticularis in a patient with SLE who had the anti-phospholipid antibody.

Flexor tenosynovitis

Flexor tenosynovitis (FTS) is a common cause of pain in the hands. It can occur as an isolated set of symptoms or it may be part of systemic diseases such as RA, SLE, PsA, gout, etc. It is often missed by general practitioners and usually mistaken for arthritis of the hand. In fact, it does not affect the PIPJ or the MCPJ, even though pain is often felt in those areas. It may manifest in a single finger, causing a nodule which leads to trigger finger **(Figure 22)**. This responds very well to injection with cortisone and local anaesthetic into the tendon sheath. The tenosynovitis may sometimes be much more extensive, involving several, if not all, the fingers. Under these circumstances, there is usually an underlying cause such as RA, SLE, or PsA. If the process is extensive, surgery may be necessary **(Figure 23)**.

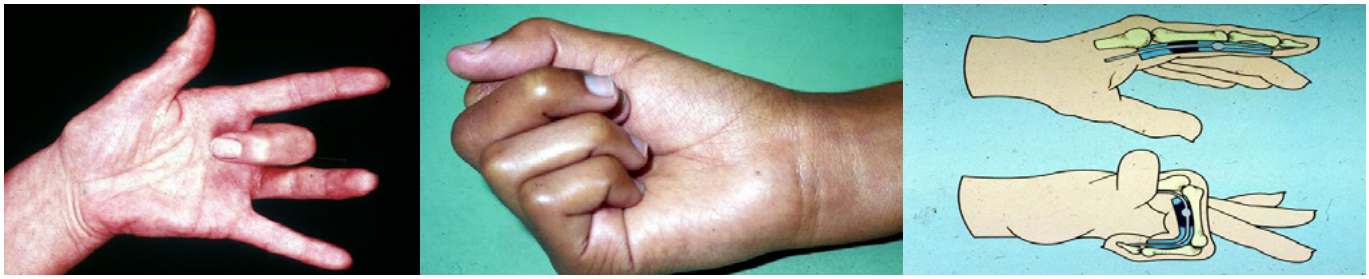

Figure 22. Flexor tendon nodules interfering with hand closure. These may also cause triggering or locking of the fingers. Injection of cortisone and lignocaine in the tendon sheath can be very effective in relieving symptoms.

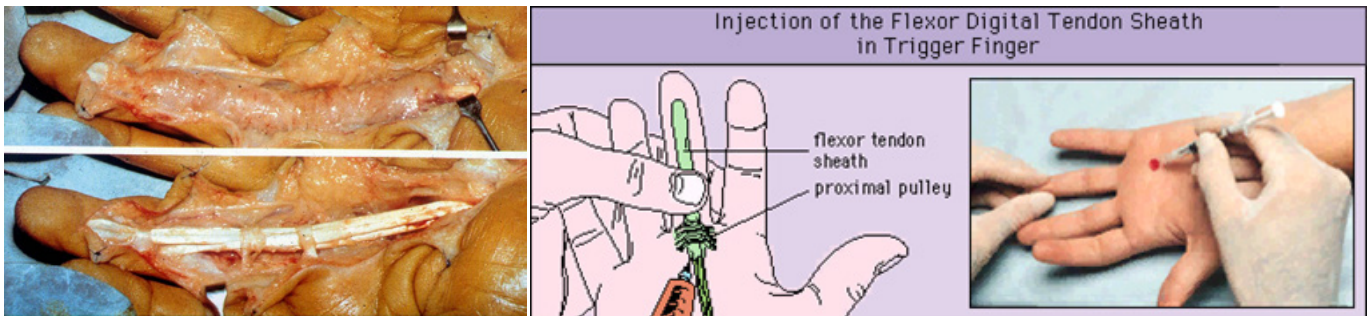

Figure 23. Diffuse flexor tenosynovitis in a patient with RA requiring surgery.

Carpal tunnel syndrome

Carpal tunnel syndrome commonly presents with symptoms in the hand. The typical symptoms include paraesthesiae in the median nerve distribution, especially at night. This is often improved by motion or hanging of the arm. The causes include pregnancy, hypothyroidism, RA, amongst others. Prolonged compression of the median nerve may result in wasting of the thenar eminence. The Tinel and Phalen signs are useful in making the diagnosis. Sometimes nerve conduction studies may be needed to confirm the diagnosis. Response to injection of cortisone and lignocaine is often effective and may produce prolonged relief of symptoms. Some patients may require surgery.

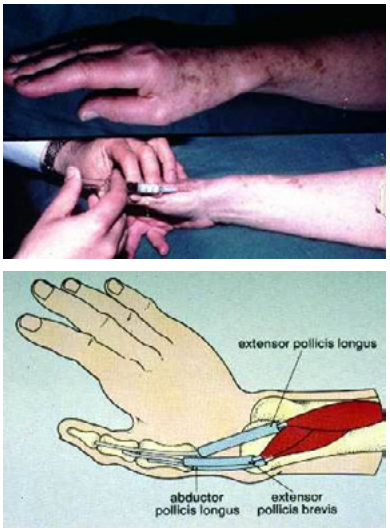

Figure 24. Anatomical structures involved in De Quervain's tenosynovitis. Injection with cortisone and lignocaine in the tendon sheath can be quite effective in relieving symptoms.

De Quervain's tenosynovitis

This is a very common cause of pain in the hand. It is usually unilateral and the patient complains of pain on squeezing, especially when opening bottles or taps. Stressing the extensor and abductor pollicus tendons by hyper-flexing the thumb at the MCPJ (Finkelstein's test) induces pain and discomfort and confirms the diagnosis. De Quervain's tenosynovitis (DQT) often coexists with OA of the CMC joint. Injection of cortisone and lignocaine into the tendon sheath provides prolonged relief and may be repeated, if necessary **(Figure 24)**.

Summary

The hands are commonly affected in a variety of rheumatic diseases and careful examination can provide several clues regarding the underlying diagnosis. The function of the hand is essentially related to flexion of the fingers and constitutes grip strength. The key to maintaining function is to retain the ability to flex the PIPJ and MCPJ. A systematic approach to the examination of the hand will ensure that the various anatomic structures such as skin, joints, tendons, nerves and blood vessels are carefully evaluated, individually and as a complex unit. The various rheumatic diseases have characteristic patterns of distribution in terms of joints, skin and function. Early diagnosis and treatment is essential in preserving adequate function, especially in RA, PsA, Gout and SSc. Physiotherapy and occupational therapy are often useful adjuncts to medical therapy.

Highlights of EULAR Congress 2020

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Attending a congress whilst sitting in your study, lounge and sometimes kitchen certainly has its advantages and disadvantages. Yes, you do miss the travel to a different city, tasting the local cuisine, and finding shopping bargains, but you do avoid running from hall to hall and feeling like you should have attended the talk next door when the one you are listening to does not meet your expectations. Being able to access all the sessions and pause, rewind and occasionally fast forward definitely is a bonus. EULAR 2020 is certainly an interesting experience. I am going to share some of the highlights of the sessions I have engaged in.

Spondyloarthritides

The spondyloarthritides had interesting discussions. Robert Landewe demonstrated in the OPTIMISE trial that it is possible to use a reduced maintenance dose of certolizumab in patients who attained remission, however, did not recommend complete withdrawal.

The PREVENT trial showed a significant and sustained improvement in signs and symptoms of patients with non-radiographic axial SpA with secukinumab. An interesting study by Mishra et al in India, showed that using a modified COBRA regimen for axial SpA showed a significant improvement in disease activity. However, in a population with many comorbidities one wonders if this is feasible?

Nissan et al (2020) showed that using a synthetic DMARD with a TNF inhibitor, improved the overall retention, using EUROSpA collaboration.

In the HOT session with Dr Allaart from the University of Leiden, she spoke about using Treat to Target as the best strategy, but also mentioned that it is possible to taper both synthetic and biological DMARDS after discussion with your patients, providing you always an open door policy should they flare.

RA and it comorbidities

The session on RA and its comorbidities drew some interesting conclusions. There is a strong risk of VTE in patients with high disease activity of RA. A multicentre study by Juge et al (2020) showed that MTX is not a risk factor for developing ILD and may be of benefit in delaying it. RA-ILD has remained well controlled with no exacerbations in over 90% of patients using TNF inhibitors.

Krebs von den Lungden-6 glycoprotein is an ELISA test and can be used as a biomarker for diagnosis and prognosis of ILD in RA. It has a sensitivity of 68% and a specificity of 83%. It is available in some countries and may be used as a prerequisite for HRCT lung scans in RA patients. This sounds promising in a country like South Africa where radiology is expensive.

The NORD-STAR study in early RA treatment of naïve patients, showed that four arms of treatment namely: Conventional therapy with MTX plus SZP and CQ and intra-articular steroids OR MTX plus steroids compared with certolizumab, abatacept or tocilizumab, all had similar outcomes, 42%, 47.8%, 52.5% and 41% respectively. This is an especially important study in emerging markets like South Africa where access to biologic DMARDS is expensive and not accessible to the majority of patients.

A large French database showed that the overall risk of malignancies did not seem to differ across the classes of biologics. They did not increase the risk of lung cancer. The French also showed an increased risk of B-cell NHL in patients with high disease activity, male gender, positive antibodies and erosions on x-rays. Of note is that MTX and other biologics were not associated with NHL.

With regards to the not yet available JAK inhibitors, they showed an increased risk of herpes zoster reactivation, as well as an elevated risk of thrombo-embolic disease in patients with risk factors for VTE disease. There was, however, data in another study showing higher drug retention with JAK inhibitors than TNF biologics.

Systemic lupus erythematosus

Michelle Petri demonstrated that Hydroxychloroquine (HCQ) blood levels are inversely associated with risk of any thrombosis in patients with SLE and can be helpful in predicting individuals at risk of maculopathy. Adjusting doses of those with higher HCQ blood levels and regular opthalmological reviews would reduce risk of maculopathy.

The 2012 EULAR/ERA-EDTA recommendations for the treatment of lupus nephritis has also been updated.

The changes include the treatment targets, use of steroids, calcineurin inhibitors, and end stage renal disease. The target of treatment is proteinuria of <0.5 -0.7g/24 hours. Induction treatment with either mycophenolate mofetil (MMF) or cyclophosphamide (EUROLUPUS) is recommended. Both are combined with pulse IVI methylprednisolone, and then oral steroids. Patients with nephrotic syndrome can be treated with high dose cyclophosphamide and tacrolimus combination. Maintenance with MMF or azathioprine is recommended. Unresponsive disease can be treated with rituximab. Class five or membranous LN can be treated with renin-angiotensin blockers, and MMF with low dose steroids.

A study by Mok et al (2016) from Hong Kong, in a long term RCT showed that tacrolimus was non-inferior to MMF as induction therapy for lupus nephritis. Another study by Chakravarty et al (2020) showed that it is possible to wean patients with quiescent lupus off MMF and only 15% experienced a mild flare.

Updated studies on neuropsychiatric SLE, showed two stages. First acute neuronal loss, and then a chronic loss of dendritic complexity. ACE inhibitors may play a role in prevention of cognitive decline. The immunosuppressive treatment guidelines for neurolupus (NPSLE) include; IV pulse steroids monthly for 3-6 months or oral daily steroids. Azathioprine is recommended for steroid sparing maintenance. Refractory disease includes treatment of psychosis, confusion and CIDP with immunoglobulin, and possibly rituximab.

Behcet's syndrome

The treatment of Behcet's syndrome by Prof Hatemi from Turkey was a nice simple easy lecture, and very informative. The recommendations for treating oral and genital ulcers, papulopustular skin lesions and arthritis are still colchicine as first choice. Refractory ulcers respond to apremilast, and also azathioprine, TNF inhibitors, IFN alpha, and thalidomide. Refractory skin lesions and arthritis should be tried on either azathioprine, IFN, TNF inhibitors but ustekinumab and secukinumab have also had some success.

It is recommended that anterior uveitis be treated with steroid eye drops and azathioprine for recurrences. Posterior uveitis is treated with steroids and azathioprine plus cyclosporine-A, and maybe IFN or TNFi. Arterial involvement is treated with cyclophosphamide and IV steroids for 6 to 12 months, and then maintained on azathioprine. Venous thrombosis is also managed with immune suppression. GIT ulcers are treated with 5-ASA, azathioprine and if severe TNFi, although these are initiated at very high doses.

Gout

Gout is still the most prevalent inflammatory arthritis worldwide and probably the worst treated disease, as most doctors don't follow treatment to target regimes for this disease. The diagnosis is not always an easy one to make. Dr Schäfer from Germany showed that both ultrasound and suspected clinical diagnosis had higher sensitivities than dual-energy computed tomography (DECT) for gout and CPPD. DECT appears to have limited utility for differentiating between gout and calcium pyrophosphate deposition disease.

The update on treatment options for psoriatic arthritis provided all the new exciting studies with new drugs. Filgotinib, upadacitinib, tofacitinib, netakimab, ilxekizumab, guselkumab and tildrakizumab all show promising data.

EXCEED, the first double-blinded head-to-head clinical trial evaluating secukinumab (300 mg) versus adalimumab (40 mg) in over 800 patients with active PsA biologic naïve patients. Secukinumab was efficacious, and showed superior results with regards to skin, but also had better retention rates.

The SELECT-PsA-1 and SELECT-PsA-2 trials have demonstrated that the JAK-1 inhibitor upadacitinib may be a promising treatment option for psoriatic arthritis patients with and without prior exposure to biologic agents. Ian McInnes (2020) reported that a "very satisfactory" proportion of upadacitinib treated patients experienced resolution of enthesitis and dactylitis.

EULAR 2021 will be held in Paris. God willing we should be over the worst of the COVID19 pandemic and be able to resume travel, and perhaps meet at the base of the Eiffel tower or the halls of the Louvre.

References

1. Mishra D. Randomized Controlled Trial of Oral Corticosteroids in Axial Spondyloarthropathy: Modified COBRA regime. Eular Poster. 2020;OP0108.
2. Juge P. Methotrexate and Rheumatoid Arthritis associated Interstitial Lung Disease. Eular poster. 2020;OP0036.
3. Lund Hetland M,et al NORD-STAR Study Group. A Multicenter Randomized Study in Early Rheumatoid Arthritis to Compare Active Conventional Therapy versus Three Biological Treatments: 24 Week Efficacy and Safety Results of the NORD-STAR Trial [abstract]. Arthritis Rheumatol. 2019
4. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. Curr Rheumatol Rep. 2011
5. Mok CC, Ying KY, Yim CW, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis. 2016
6. Chakravarty E, Utset T, Kamen DL on behalf of ALE06 Working Group, et al OP0167 SuccessfulL withdrawal of MMFin quiescent SLE: results from a randomised trial Annals of the Rheumatic Diseases 2020

Biosimilars in South Africa

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The use of biologic disease modifying drugs (bDMARDs) has made an impact on the outcome of rheumatic diseases that would have seemed impossible thirty years ago. For the first time, we as rheumatologists, are able to really change people's lives and suppress diseases like rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and other connective tissue diseases to an extent where damage is minimal and function can be restored.

This has had short- and long-term benefits for individual patients and improved overall outcomes. The downside of this is that the technology used is expensive and this translates to expensive medication, which has meant that access is limited, particularly in a resource constrained country such as South Africa. Most of the use is by patients on private medical aids and even there it is only by patients on the highest level of medical cover and public sector access is almost non-existent.

A further driver of the cost of any original drug is the amount that is spent on research and development of the drug. When the molecule is first registered, before it starts the long and expensive journey to registration and use, there is a patent on the molecule and while this is still valid, there is a chance to recoup research and development costs by the company that has brought the drug to market. When this expires, other companies can produce copies of the drug. A number of originator biologic drugs have or are going to lose their patents, which will give other companies a chance to produce so-called biosimilar or similar biotherapeutic products. A biosimilar is defined as a biotherapeutic product that is similar to (has an absence of relevant differences from) an already licensed reference biotherapeutic or bio-originator, in terms of efficacy, safety, purity and potency.

The potential benefit of biosimilar medication is that there will be a greater variety of options for healthcare providers and patients at a more affordable cost. The use of biosimilar products are expected to save healthcare funders billions around the world, but a biosimilar is different to a generic of a chemical originator drug and this has led to many questions around these drugs, which can be associated with a hesitancy in prescribing them.

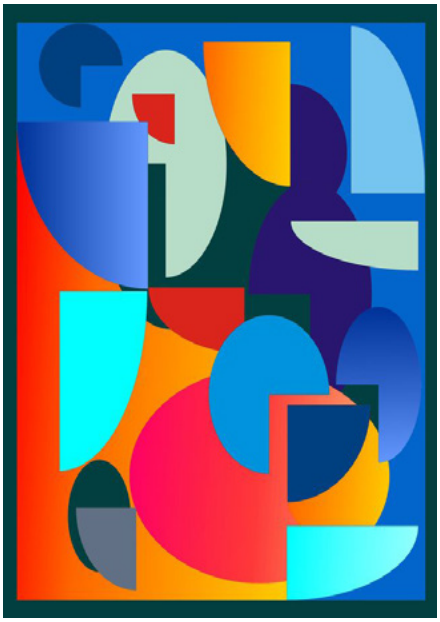
There is a fear of these drugs being of a lower quality. Uncertainty about the concept of these drugs being "similar but not identical". A concern about safety not being properly established or about immunogenicity which can be caused by a small difference in a drug. These are important concerns, but for funders, economic concerns are probably paramount and they can and have insisted on the use of biosimilars to save money. This raises ethical dilemmas as this can be done with the prescriber's input, where the biosimilar is interchanged with the originator drug, but can also just be substituted without the consent or knowledge of the prescriber. Unfortunately, especially with the initial information or lack of knowledge that we had about biosimilars, negative sentiment led to what is coined as the "nocebo effect". This causes the patient and doctor to doubt the drug in terms of efficacy or tolerability and the patient to feel worse or imagine adverse effects of the drugs.

The first biosimilars have been registered in South Africa this year and this will hopefully mean that there will be a chance to give biologics to more of the many patients that need them. To be able to make a more considered decision about the prescription of biosimilars, we need to understand biosimilar development from manufacture to the process followed for biosimilar approval. We also as the South African rheumatology community need to have a position statement in place with regards to the use of biosimilars and make sure that we improve our systems for pharmacovigilance with their introduction.

The manufacturing process for a biologic or biosimilar, is highly specialised and controlled. A gene is spliced into a host cell that will then produce these proteins. These cells need to be nurtured so that the cell line can expand and produce the drug that is eventually recovered and purified. Even though the patent has expired on a biologic, there may be proprietary steps in the manufacturing process that are not known to the manufacturer of a biosimilar. Small differences in the process can change the product, causing differences in structure or microherterogeneity of the drug. This is not so much an issue with the sequence of amino acids that make up the protein molecule, but there can be several post translational changes that occur. This may be enough to change the nature of the drug with, for example, resultant immunogenicity in the user, a difference in pharmacokinetics or stability of the structure of the drug. The World Health Organisation (WHO) guidelines on evaluation of Similar Biotherapeutic Products (SBPs) states: "Decision making regarding the licensing of SBPs should be based on scientific evidence. The onus is on the manufacturer of a SBP to provide

the necessary evidence to support all aspects of an application for licensing". Biosimilar testing needs to show that the product is identical to the originator in terms of structure, composition and in-vitro activity." In South Africa, The South African Medicines Control Council (the MCC), which is now the South African Health Products Regulatory Authority (SAHPRA), published guidelines for the testing and registration of biosimilars in South Africa and all companies registering biosimilars follow this. It states "The original registered reference medicine is manufactured and controlled according to non-public proprietary methods that are not available to a "follow-on" developer; therefore it is necessary that the applicant for a biosimilar medicine (that may use alternative production technologies) provide evidence that the biosimilar is indeed similar in quality, safety and efficacy to the registered medicine used as reference product."

The testing process starts with the physicochemical characterisation of the biosimilar. It must show that the biosimilar is identical to the bio-originator in terms of primary structure as well as higher order structures. These are the changes that occur with post-translational modifications of the protein resulting mainly from glycosylation, but also from deamination and oxidation. Non-clinical, in vitro studies are done to make sure that antigen binding affinity and avidity is the same in the biosimilar as the bio-original. After this the different phases of in vivo testing are conducted. Animal studies may be conducted and then randomised controlled trials are done to establish equivalence in pharmacokinetics and clinical efficacy. This phase of testing is less intense in terms of patient numbers that need to be enrolled compared to the trials done for bio-originator testing, but this is because it is assumed that if all physiochemical and in vitro data show equivalence between the bio-originator and biosimilar, then clinical benefit can largely be assumed. Similarly, even though the biosimilar is only tested in one indication, registration of the biosimilar will be for all the diseases for which the bio-originator is registered for by means of extrapolation between indications. This is allowed by regulators if the mechanism of action is the same in the different diseases. This has been an area of concern for clinicians, but there is little evidence to suggest that extrapolation cannot be successful. We are getting more and more data as well from registries around the world that give us real world evidence about biosimilars and this is important as they supplement the information from the smaller clinical trials for registration.



The decision to give any biologic or biosimilar is a shared decision between the treating rheumatologist and the patient based on what is the most appropriate treatment for that patient.

The first biosimilars now have registration in South Africa. There is a biosimilar infliximab, Remsima® and a biosimilar adalimumab, Amgevita™. The South African Rheumatism and Arthritis Association's (SARAA) position statement on biosimilars in South Africa is the following: "SARAA is committed to maintaining the highest standard of care for patients with rheumatologic disease against the background of a country, which is resource constrained. To this end we welcome the registration of the biosimilars in South Africa and hope that the reduction in price for treatment will mean that more patients that are in need of treatment, will be able to access it. The decision to give any biologic or biosimilar is a shared decision between the treating rheumatologist and the patient based on what is the most appropriate treatment for that patient. We are opposed to the automatic substitution of any drug that has been specifically prescribed for a patient, whether it is an originator or biosimilar therapy". SARAA runs a registry where biologic use is captured in South Africa and this will also help us to trace any issues that might be a specific problem for us such as the incidence of tuberculosis.

In summary, biosimilars are an exciting addition to our available drugs to prescribe to our patients. There are questions around these drugs, but these are well addressed by the rigorous testing and trial evidence that we have. We look forward to being able to give their benefit to our patients.

References

1. Kay J, Schoels MM, Dörner T, Emery P, Kvien TK, Smolen JS, Breedveld FC; Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Task Force on the Use of Biosimilars to Treat Rheumatological Diseases. Ann Rheum Dis. 2018 Feb;77(2):165-174.
2. World Health Organisation. Guidelines on evaluation of similar biotherapeutic products (SBPs): WHO press
3. Kay J, Isaacs JD. Clinical trials of biosimilars should become more similar. Ann Rheum Dis 2013;72:315-8
4. Isaacs JD et al. The biosimilar approval process: how different is it? Considerations Med 2017;1:3-6
5. Medicines Control Council. Biosimilar medicines quality, non-clinical and clinical requirements. Aug 2014.

Rheum Lites

Rheumatologists on the frontline against COVID-19

Take a look at some of our rheumatologists working in COVID-19 units. From left to right: Dr Anita Lai (Netcare Waterfall), Dr Gisela van Rooyen (Unitas Hospital) and Dr Kavita Makan (CHBAH)

RheumQUIZ

Answers to case study questions on page 12

1. Thrombosis, cytokine release syndrome, Myocardial ischaemia, myocarditis, Takotsubo cardiomyopathy, arrythmias, encephalopathy, GBS, strokes, AKI, proteinuria, haematuria, transaminitis, DKA, livedo reticularis, pernio.
2. IL1 and IL6 inhibitors. Anecdotal benefits have been reported with these drug classes. Markers of hyperinflammation or cytokine storm:
   a. Clinical: high grade fevers, hypotension, multi-organ dysfunction.
   b. Laboratory: Elevations in ESR, CRP, ferritin, Il-6, LDH
3. Pulmonary aneurysm

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Biotechnology-based medicines serve an increasingly critical role in fighting serious diseases.[3] With advances in biotechnology, these therapies are being utilised for an increasing number of conditions.[3] As newer biologics come to market, the patents of the first wave of biologics are beginning to expire.[3]

Amgen's extensive experience in biologic development and its capabilities in biotechnology manufacturing have positioned it as a global leader in the development of biosimilar products.[3]

Biosimilar products are highly similar to the reference biological with respect to critical quality attributes and should have no clinically meaningful differences with respect to safety, purity and efficacy.[5] Amgen currently has multiple biosimilar products in development in therapeutic areas that include oncology and inflammation.[3]

For more information on Amgen, please refer to https://www.amgen.com/ or contact Amgen South Africa.

Reference: 1 About Amgen. Fact sheet. Available from: https://www.amgen.com/~/media/amgen/full/www-amgen-com/downloads/fact-sheets/fact_sheet_amgen.ashx. [Accessed 11 March 2020].
Amgen South Africa (Pty) Ltd., Co. Reg. No.: 2011/112148/07. Building D, Ballyoaks Office Park, 35 Ballyclare Drive, Bryanston Ext. 7, 2021; Tel: 011 100 5300 Fax: 011 100 5301 Adverse Event Reporting Email: safety-south-africa@amgen.com.

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References:
1. AMGEN Fact Sheet. C2020. Accessed 25/3/2020. Available from https://www.amgen.com/about/quick-facts/ **2.** AMGEN Biotech. C2017. Accessed 25/3/2020. Available from https://www.amgenbiotech.com/manufacturing-innovation.html **3.** AMGEN Our Strategy. C2017. Accessed 6/4/2020. Available from https://www.theamgendifference.com/our-strategy.html **4.** AMGEN Corporate Brochure. C2016. Accessed 17/4/2020. Available from https://www.amgen.com/-/media/amgen/full/www-amgen-com/downloads/amgen_corporate_brochure.ash **5.** Kaur P, Chow V, Zhang N, *et al.* A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab. *Ann Rheum Dis* 2017;76:526-533.

Amgen South Africa (Pty) Ltd., Co. Reg. No.: 2011/112148/07. Building D, Ballyoaks Office Park, 35 Ballyclare Drive, Bryanston Ext. 7, 2021. Tel: 011 100 5300 Fax: 011 100 5301. Adverse Event Reporting email safety-south-africa@amgen.com. Expiry Date: April 2022. PR-AMV-ZAF-000023.

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Reference: 1 About Amgen. Fact sheet. Available from: https://www.amgen.com/~/media/amgen/full/www-amgen-com/downloads/fact-sheets/fact_sheet_amgen.ashx. [Accessed 11 March 2020].
Amgen South Africa (Pty) Ltd., Co. Reg. No.: 2011/112148/07. Building D, Ballyoaks Office Park, 35 Ballyclare Drive, Bryanston Ext. 7, 2021. Tel: 011 100 5300 Fax: 011 100 5301 Adverse Event Reporting Email: safety-south-africa@amgen.com.

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