Evening Medical Update: A run-through of Rheumatology
May 2022

Understanding biologics and targeted synthetic disease modifying drugs – Dr Nicola Gullick, Clinician Lead & Consultant Rheumatologist, University Hospitals Coventry & Warwickshire NHS Foundation Trust

Are JAK inhibitors considered immune suppressors?
Yes, absolutely. They can potentially inhibit multiple cytokines and cell types, so are likely to be broader immunosuppressives than biologics, but are also short acting

What are the issues regarding development of antibodies to these medication during their use?
In part it depends on the antibody type (neutralising vs non neutralising) but in general

- Reduced serum levels (increased elimination) and reduced efficacy
- Adverse events – injection site or infusion reactions – rashes, serum sickness like reaction

Concomitant methotrexate appears to reduce antibody production

Who keeps the registries? Are all patients on biologics added to them? Or is it all patients with RA, Lupus etc..?
They are usually run by academics as research studies, and there are separate registries (at least in the UK) for SLE (BILAG-BR), PsA (BSRBR-PsA), RA (BSRBR), UKI-VAS (vasculitis), MYO_ACT (myositis). The AS register is now closed. The registries aren't set up at all trusts, but where they are, patients are approached, but it isn't compulsory to take part. The caveat (in England anyway) for NHS-England direct funded drugs (lupus/vasculitis/myositis) is that the expectation to enrol a patient is much higher unless they are unable to consent e.g. due to language barrier or neuropsychiatric disease

Dr Gullick - would the PCT be raised if the CRP is suppressed?
Yes, but isn't routinely available at all trusts – I certainly don't have access.

Dr Gullick - I saw a patient on certrolizumab in cardiology clinic who had developic apical HCM. Cardiomyopathy is listed as a side effect - but not specified which type. Do you know any if there's any data on that?
There are published case reports, most of the ones I have read are dilated CM

Should patients temporarily pause treatment after covid vaccine?
Good question, partly depends on the treatment. There is a recently completed study on temporarily stopping methotrexate (for 2 weeks) post covid vaccines which hasn't reported results yet but will be reporting very soon.
There is data supporting this approach for flu vaccine
For biologics – no
JAKi – could be potentially useful.
The balance is risk of flare vs better vaccine response. If a patient flares and this results in being given moderate dose steroid, that will also blunt vaccine response.
For rituximab – for all vaccines we advise giving at least 4 months after last dose (it's given 6 monthly usually and B cells will start to repopulate around this point on average) and then wait at least 4 weeks before the next cycle. For covid vaccines, particularly as mortality of covid in RTX treated patients was higher than all other biologic, we delayed cycles to let patients get their vaccine. This included expediting doses during the primary vaccine course – rather than waiting for 12 weeks.
In general, better to get all relevant vaccines updated pre-treatment, but for the yearly ones it's more a question of timing.

Hi do u recheck covid antibodies before B cell therapy rituximab ?
No, at least not in my trust. Most patients are on rituximab as there are limited treatment options due to comorbidities e.g. lung disease and the alternative would often be high dose steroid. We do engage with patients and inform them of the increased risk, and reduced likelihood of vaccines being effective

How common are Methotrexate induced lung complications
Extremely rare. I've seen 3 patients in the last 20 years – and probably >10,000 patients on MTX. There was a study specifically looking for those patients about 10 years ago – it was abandoned as there weren't enough patients. RA associated lung disease is definitely more common

Hi Dr Guillick , Thank you for very good presentation. If someone's IGRA is positive and CXR is positive for TB. Do we need to start anti-TB treatment and at the same time continue biologics? or we need to start biologics after stopping anti TB treatment . Thanks
Yes, we would commence TB treatment. Timing of starting biologics would vary by agent. For anti-TNF usually wait at least a month before starting, but for other biologics where TB reactivation would be less common you could start concurrently (ustekinumab/anti-IL-17). JAKi – less clear but I think a month would be reasonable.

What is the name of the book for Immunology
I'd answered this one already
Cellular and molecular Immunology by Abbas and Lichtmann
The same authors have also written Basic Immunology but it was the previous book that I have experience of using

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Clinical cases in Rheumatology – Dr Helen Harris, Consultant Rheumatologist, Western General Hospital, Edinburgh

Dr Harris - do you recommend 2 week pause of MTX for all vaccines or just covid? Does this also apply for mycophenolate?

2 week pause of MTX for all vaccines – flu, pneumovax and C19
Data weaker for MMF and other DMARDS like Azathioprine but if patient is well controlled suggest 2 week pause of AZA and MMF

What is stroke risk of biologics? Which is at high risk ?

The latest meta analysis presented at BSR showed that active RA significantly increases CVA risk. TNFi drugs lower this risk significantly. JAKi drugs lower this risk slightly less than TNFi

All treatments that reduce inflammation reduce CVA risk more than leaving patient untreated.

Dr Harris biological agents will impact upon type 1 autoimmune diabetes too ? *Sorry I am not able to give expert answer on this but -*

Excerpt of article to answer question – ref

Cold Spring Harb Perspect Med. 2012 Aug; 2(8): a007716.

doi: 10.1101/cshperspect.a007716

PMCID: PMC3405831

PMID: 22908194

Clinical Immunologic Interventions for the Treatment of Type 1 Diabetes

Lucienne Chatenoud,[1] Katharina Warncke,[2,3] and Anette-G. Ziegler[3,4]

Therapies such as CTLA4-Ig (Abatacept) (Orban et al. 2011) that block costimulation, or CD20 monoclonal antibody (Rituximab) that reduce B-cell contribution to autoimmunity (Pescovitz et al. 2009) have resulted in significant improvement of β-cell function, at least short term. Pilot trials with anti-inflammatory drugs have shown similar promising effects (anti-TNF, IL-1Ra ...). Vaccination with autoantigen has been shown to alter antigen-specific immunity and initial studies reported some preservation of β-cell function (Ludvigsson et al. 2008). However, these observations were not confirmed in more recently reported phase II and III studies (Wherrett et al. 2011). Strategies using short treatment (1–2 wk) with monoclonal antibodies to CD3 that interfere with pathogenic T-cell activation provided encouraging results in both academic phase II trials (Herold et al. 2002, 2005; Keymeulen et al. 2005, 2010) and in a recently reported phase III study (Sherry et al. 2011). Efficacy, as assessed by maintenance of β-cell function and decrease in insulin needs was observed, depending on the study, for 1–4 yr after the end of treatment. Finally, more aggressive treatment with lymphoablation followed by autologous hematopoietic stem cell transplantation appears particularly effective with reports of medium-term T1D reversal (Voltarelli et al. 2007; Couri et al. 2009).

How much percentage of patients with Ankylosing spondylitis can have complete remission or autoremission?

Here is a good summary:

Poddubnyy D, Gensler LS. Spontaneous, drug-induced, and drug-free remission in peripheral and axial spondyloarthritis. *Best Pract Res Clin Rheumatol*. 2014;28(5):807-818. doi:10.1016/j.berh.2014.10.005

- Remission is an attainable treatment target in patients with Spondyloarthritis with the majority of data coming from clinical trials in axial Spondyloarthritis and observational studies in peripheral Spondyloarthritis.
- Drug-induced remission can be achieved in up to a third of the patients with axial Spondyloarthritis treated with NSAIDs and in up to a half to two-thirds of the patients treated with TNFα inhibitors, especially if the treatment is initiated early (within first 3–5 years of disease).
- Discontinuation of anti-TNFα therapy upon achievement of the remission in Ankylosing Spondylitis leads to disease flare in the majority of patients within 12 months after treatment cessation. Increased drug intervals and/or dose reduction may be an alternative to complete drug discontinuation for patients in remission. The same may be true for patients with non-radiographic Axial Spondyloarthritis, but more data are needed to confirm this.
- Reactive arthritis as a form of peripheral Spondyloarthritis is characterized by a high rate of spontaneous remissions, while data on the use of antibiotics for remission induction in acute and chronic arthritis are controversial.

Dr Harris: Does post-vaccine methotrexate not have any suppressive effect on the immunity obtained after Covid vaccine?

No – as soon as the B cell clones responding to C19 have been formed and the anti bodies have been made MTX can be restarted (in 2 weeks). MTX acts at the point where new B Cell lines are made in the BM – once they are made MTX cannot stop them.

Dr Helen - Does it matter what kind of exercises are undertaken - isometric or isotonic? and would there be a preference for a particular presentation or rheumatological disease condition?

All rheumatology conditions benefit from exercise – even when inflammation is active.

My understanding is that PRT is iso tonic – the reps are carried out at 80% of maximum lifting ability – the weights can be increased as strength increases.

Please see Prof Andrew Lemmy Bangor research for further information