

Questions for Birdshot Day no 4, November 2018

Here are answers to some of the questions you asked before the Birdshot Day.

Biologics and biosimilars, including Humira

1. Apart from price, what are the key differences, if any, between Humira (and other biologics) and their new biosimilars which are being introduced?

This is not yet known. No obvious problems have been seen in rheumatoid arthritis patients who have swapped to biosimilars. A few birdshot patients who have moved from original infliximab to infliximab biosimilars have relapsed.

2. Humira is a very powerful drug with potentially fatal side effects. What is the long-term course and at what point in the treatment does one suggest reducing the frequency of the dosage?

In birdshot, we would look to achieve about two years of stability on Humira treatment with no flares, stable visual fields and ERGs, then the time between injections could be increased. Steps could be: 40mg every 21 days, then 40mg every 28 days, then stop, or possibly step down to a 20mg dose.

3. Can you tell me what the Humira blood tests values mean? Why could they be so low in my case even though I inject it weekly?

This might be due to antibody formation against the Humira. The UK blood test ranges for blood drug levels and for measuring antibodies are:

- Adalimumab blood drug levels (in micrograms per ml)
 - Minimum 'trough' level (ie, taken just before the next dose is due) = 4.9 micrograms per ml.
 - In rheumatoid arthritis, levels between 5 and 8 micrograms per ml were associated with a good response to treatment, suggesting that no extra improvement could be expected by increasing the dose (ie, by reducing the time interval

between injections) in patients with a 'trough' level of more than 8 micrograms per ml.

- Anti-adalimumab antibodies (in nanograms per ml)
 - Negative: less than 10 nanograms per ml
 - Positive: more than 10 nanograms per ml

4. I would like to ask why they recommend Humira over Actemra (Ro-Actemra; tocilizumab)? I have been on Actemra for 4 years and just curious why Humira is preferred over Actemra.

This is because Humira has gained US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for treating non-infectious intermediate, posterior and panuveitis in adults and children aged 2 years and over. Humira is the first and only biologic therapy approved for uveitis so far. Actemra has not been specifically evaluated clinically for treating uveitis, except for a study (APTITUDE) in juvenile idiopathic arthritis-associated uveitis. However, there is a small amount of evidence that Actemra can be helpful in uveitis, particularly for patients who have chronic macular oedema related to their uveitis.

Intravitreal methotrexate

5. I'm curious about the potential use of intravitreal methotrexate injections to stop inflammation and macular oedema. I saw someone in another group I'm in say she got into remission using that treatment.

There is not a lot of evidence about this. A few small studies show it appears to be effective and it may give longer remission than intravitreal triamcinolone acetonide injection. Some reports indicate its potential for treating uveitic macular oedema. Also, in US, the MERIT clinical study is currently being undertaken to compare the efficacy of intravitreal methotrexate, the anti-VEGF injection Lucentis (ranibizumab) and dexamethasone intravitreal implant in uveitic macular oedema.

Intravitreal sirolimus

6. Would love to know the potential for intravitreal sirolimus.

Sirolimus has anti-inflammatory and immunosuppressant actions. It has been studied in clinical trials for treating intermediate, posterior and

panuveitis. Because of some design flaws in the study leading up to possible marketing, the US FDA did not grant approval for the use of intravitreal sirolimus in uveitis.

Suprachoroidal injections of triamcinolone

7. What is the latest on suprachoroidal injections of steroids (Clearside Biomedical trial) to avoid side-effects of intravitreal steroids or systemic medicines?

Clearside Biomedical <http://www.clearsidebio.com/programs.htm> has shared positive results from its PEACHTREE trial which studied the safety and tolerability of suprachoroidal placement of triamcinolone for uveitic macular oedema. If final results are good, Clearside's 'Eyevensis' EyeCET would be the first approved technology to treat uveitis-related macular oedema. However, this technology is being used to deliver a steroid to the eye tissues, with the typical steroid side-effects of raised intraocular pressure and cataract formation, but these side-effects appear to be slightly less frequent with the suprachoroidal route than with the intravitreal route.

<https://www.birmingham.ac.uk/news/latest/2018/07/age-related-macular-degeneration-eyedrops.aspx> describes work in progress to develop eye drops to treat age-related macular degeneration, rather than the current treatment by injections into the eye. Though not directly applicable to treating birdshot, this shows that work is ongoing to try to get medications to the back of the eye by using eye drops.

Steroids

8. What can you tell me about treating birdshot with Acthar gel?

Acthar gel, also known as HP Acthar gel, contains ACTH (adrenocorticotrophic hormone). It stimulates the body's adrenal glands to produce corticosteroid hormones. There is only one recent relevant paper - a single case report (2016) - but a study of Acthar in uveitis has recently started in US. <https://clinicaltrials.gov/ct2/show/NCT03656692> Acthar now costs more than US\$40,000 a vial.

9. Steroid dose reduction - any hope of having national/international broad guidelines on this, particularly on how to taper doses of under 7.5mg/day of prednisone or prednisolone, plus more awareness by the medical profession of the common side-

effects experienced once the dose goes below 7.5mg/day? These effects are both unexpected and troublesome, and patients should routinely be given advance information on what they may experience. Also, explanation of the use and purpose of the 'short Synacthen test' for checking adrenal function - when is this test indicated, what do the results mean, and what treatment is then recommended if adrenal function is found to be low?

There are numerous steroid-tapering guidelines and recommendations. There is insufficient evidence to support any particular withdrawal regimen, so the rate of withdrawal should depend on:

- the person's response to the withdrawal (if withdrawal symptoms are reported, resume a higher dose and continue the withdrawal at a slower rate),
- the condition being treated,
- the intended length of treatment.

Short Synacthen test: the purpose of this test is to diagnose adrenal insufficiency: a condition where there is reduced production of the body's own adrenal hormones. Normally, the body's pituitary ACTH hormone stimulates the secretion of cortisol from the adrenal glands. Synacthen (a synthetic ACTH called tetracosactrin) has a similar effect. However, in patients with adrenal insufficiency, there is an inadequate response to the ACTH injected in the Synacthen test.

A common cause of adrenal insufficiency is treatment with steroids (glucocorticoids) such as prednisolone. If the short Synacthen test result indicates adrenal insufficiency, this is usually treated with hydrocortisone or by continuing the prednisolone.

10. Should high doses of prednisolone/prednisone be considered safe to treat birdshot if that patient is also diagnosed as diabetic and is a glaucoma suspect?

As with any treatment, it is a balance between risk and benefit.

Supplements

11. What supplements or complementary therapies have birdshotters used in combination with their medical regime, and what works?

No trials have been undertaken on this.

12. *Is it worth taking supplements, eg, turmeric?*

No trials have been undertaken on this.

Medicines side-effects

13. *What are the long-term side-effects of mycophenolate mofetil?*

These are well documented online.

Birdshot

14. *How do I get this condition into remission?*

At the moment, by a combination of immunosuppressant/biologic/steroid.

15. *Does the condition lead to permanent blindness or just visual impairment?*

In theory, visual impairment rather than true 'blindness' (total sight loss).

16. *Have there been any developments to reverse the condition or can it only be slowed down?*

It can possibly be reversed with aggressive therapy if diagnosed early, otherwise treatment is aimed at slowing it down.

17. *What about common co-morbid conditions associated with birdshot?*

None that are well recognised.

18. *Are there links between birdshot and bodily aches and pains or illnesses or other conditions, eg, osteoarthritis of hip, and also hearing loss?*

No. Treatment side effects could cause similar problems.

19. *Why do my visual field numbers keep going down, despite aggressive treatment and no obvious inflammation or flare or active cells?*

Is your 30Hz implicit time on your ERG tests getting worse?

20. *Is it ever recommended to take a sample of eye fluid and test it for microorganisms that might be triggering an autoimmune response? If so, what tests are used?*

This has probably been done, but what microorganisms would you test for? The viruses, bacteria and parasites that can cause retinal infection do not give an eye picture that looks like birdshot.

21. *My doctors are uncertain as to whether my early/mild birdshot should be treated with immunosuppressants. They can't find evidence that this works and how long one must be on these drugs to possibly achieve remission. No good studies are available. We need a global database where doctors can input their results and researchers can tabulate. Please, let's work on this.*

The Birdshot ABC Birdshot Data Registry and Birdshot Biobank is beginning this work for UK patients.

22. *Is there anything in common among birdshot patients who are in long-term, medication-free, durable remission? This includes biomarkers (body mass index, cortisol, HbA1c, white blood cell counts, toxins, etc) to diet (sodium intake, animal products, etc) to stress management, sun exposure or anything else?*

Answer is probably no, unless some patients have milder and others have more aggressive forms of the disease, which could be related to slightly different genetic profiles.

23. *Glen Jeffery wrote about 'Red Light influence' 670 nm light wave length. Is there any more information regarding this therapy and if it works?*

In addition to the answer given by Chris Hogg at the Birdshot Day (Session 6), see

<http://dx.doi.org/10.1016/j.neurobiolaging.2017.01.001> for more information.

Genetics

24. Regarding genetics, the mutation of the HLA-A29 gene is a common thread amongst birdshot patients. Is it possible that the mutation is caused by environmental factors such as chemotherapy?

It is not HLA-29 that will be mutated. HLA-A29 is a leucocyte antigen, but as with all proteins, it is encoded by a gene. These genes are not mutated throughout life.

While there are different forms of HLA-A29 (A29.01 and A29.02) these differences are not caused by environmental factors. HLA molecules are defined at conception, with children having a combination of HLA molecules from both parents. However, when the body is affected by environmental factors, HLA-A29 may give a specific response to these challenges, and this is involved in birdshot uveitis.

Response to environmental factors is known as epigenetics: this is when certain genes may be switched on or off in response to challenge. If this response gets out of control, then it can lead to inflammation.