Identifying rheumatic disease patients at high risk and requiring shielding during the COVID-19 pandemic

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Rheumatology teams care for patients with diverse, systemic autoimmune diseases who are often immunosuppressed and at high risk of infections. The current COVID-19 pandemic has presented particular challenges in caring for and managing this patient group. The office of the chief medical officer (CMO) for England contacted the rheumatology community to provide expert advice on the identification of extremely vulnerable patients at very high risk during the COVID-19 pandemic who should be ‘shielded’. This involves the patients being asked to strictly self-isolate for at least 12 weeks with additional funded support provided for them to remain at home. A group of rheumatologists (the authors) have devised a pragmatic guide to identifying the very highest risk group using a rapidly developed scoring system which went live simultaneous with the Government announcement on shielding and was cascaded to all rheumatologists working in England.

Introduction

The first UK cases of COVID-19 were reported in February 2020, initially in those returning from abroad, and by early March the disease was spreading rapidly in the UK. With the NHS, and ITU beds in particular, coming under increasing pressure the Government set in place measures including social distancing and self-isolating to slow the progress of the disease. The next step was to ‘shield’ the extremely vulnerable patients (both adults and children) from the disease, aiming to protect the 1.5 million highest-risk patients across England. To put this in context, 17.5 million people in England are eligible for the seasonal influenza vaccine each year. The figure of 1.5 million was a number determined by NHS England and the chief medical officer (CMO), taking into account the resources available to provide additional support to these most vulnerable individuals. To draw up parameters for shielding, the government enlisted the help of experts in the field and drew up a list of conditions felt to be at highest risk. This included individuals on immunosuppression therapies sufficient to significantly increase the risk of infections (such as SCID, homozygous sickle cell) individuals with specific cancers (leukaemia, lymphoma or myeloma) or on active chemotherapy, radical radiotherapy or targeted immunotherapy individuals with severe respiratory conditions including cystic fibrosis, severe asthma and severe COPD individuals with rare diseases and inborn errors of metabolism that significantly increase the risk of infections (such as SCID, homozygous sickle cell) individuals on immunosuppression therapies sufficient to significantly increase the risk of infection pregnant women with significant heart disease, congenital or acquired.

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NHS Digital was able to identify 900,000 of these individuals through interrogation and analysis of multiple national datasets including Hospital Episode Statistics (HES) and Primary Care Prescribed Medicines (PCPM), but recognised it needed the help of the medical specialties to identify the remainder. The representative specialist medical societies were contacted, which included the British Society for Rheumatology (BSR).

We were given a clear steer by the CMO that these patients should represent the most vulnerable and the overall envelope across England should be kept within the 1.5 million target to ensure that resources were directed to the most in need. It was also very early on that all the specialties needed to come to a consensus to avoid disparity between the groups being identified.

Process

A decision was made to define three groups of individuals – the extremely vulnerable who should be advised to ‘shield’, an intermediate group at moderate risk who should self-isolate only if there were particular concerns or high-risk circumstances, and a low-risk group who did not need to self-isolate. The decision to define three groups of individuals was based on work already done by the Public Health England ‘Immunosuppressed cell’ group, where they had divided individuals into three groups based on their perceived vulnerability. Post-publication, the intermediate group caused confusion among patients and doctors and we changed the title of the group to ‘Patients to self-isolate or maintain social distance at their discretion’. The aim was to allow some flexibility in the application of the guideline to take individual circumstances into account. This would include, for example, specific co-morbidities (such as interstitial lung disease) which might be felt to lead to greater vulnerability, or particular circumstances, such as working in face-to-face healthcare settings which might increase the risk of exposure to COVID-19.

In determining the group at very high risk, we considered the limited available evidence on the different groups of immunosuppressive drugs and their potential to increase risk during the COVID-19 pandemic. We also considered the effect of comorbidities on disease susceptibility and outcomes. Although children and young people appear to be at lower risk on the current very limited evidence, our aim was that our advice should apply to all ages.

COVID-19 and immunosuppressive drugs

At the time we were drawing up our stratification guide, there were emerging data from China about the characteristics of COVID-19 cases. A study of 1,099 confirmed cases in Wuhan identified only two patients with immunodeficiency and there has since been a reassuring report from Italy on a cohort of 320 patients with rheumatic disease on both conventional DMARDs and biologics in whom only one required hospitalisation and none died. Many of the existing biologic registers have started recording cases of COVID-19 in patients on immunosuppressive drugs. Cases reported to date include (T Youngstein, personal communication):

- a 23-year-old male with Crohn’s disease on infliximab with mild disease who did not require hospitalisation
- a 53-year-old female with Crohn’s disease on adalimumab who was hospitalised but did not require ventilator support
- a female with ulcerative colitis (age unspecified) on tofacitinib and steroids who did not require hospitalisation.

Given the paucity of evidence in this area we decided to adopt a precautionary approach and presume that immunosuppressive drugs would increase susceptibility to COVID-19.

Corticosteroids

A systematic review of observational studies of corticosteroids in patients with severe acute respiratory syndrome (SARS) was unable to find any conclusive evidence of benefit but found some evidence of delayed viral clearance and side effects, including diabetes mellitus, psychosis and avascular necrosis, in the corticosteroid treatment groups.

While randomised controlled trials (RCTs) of corticosteroid use in rheumatic diseases have not reported an increased risk of infection, data from registries and observational studies have pointed to a consistently elevated risk of infections (both serious and opportunistic). Patients with rheumatic diseases treated with high-dose corticosteroids are at significant risk of serious infection. A cohort study of more than 15,000 patients over the age of 65 years with rheumatoid arthritis (RA) who were receiving disease-modifying anti-rheumatic drugs identified glucocorticoids as a significant risk factor for bacterial infection. Glucocorticoid use doubled the rate of serious bacterial infections as compared with methotrexate use, with a clear dose-response relationship for dosages $\geq 5 \text{ mg/day}$ and for $\geq 20 \text{ mg/day}$. These findings were confirmed in a retrospective RA cohort, age $\geq 66$ years, from Ontario where the drug category with the greatest effect estimate was glucocorticoids, which exhibited a clear dose response with an odds ratio ranging from 4.0 at low doses to 7.6 at high doses.

In light of this evidence, we decided that high dose corticosteroids (defined as $\geq 20 \text{ mg per day}$ for more than 4 weeks or 0.5 mg/kg for children) would constitute a very high risk. We had initially considered $\geq 15 \text{ mg daily}$ for 4 weeks, which was in line with the dose considered high risk by the ‘Immunosuppressed cell’ group, but it soon became apparent, following discussion among the group and discussion with other speciality groups, that 20 mg (0.5 mg/kg for children) was felt to be a more realistic threshold for very high risk. This also brought us in line with the BSR biologic safety guidelines which recommend immunisation for patients on $\geq 20 \text{ mg of corticosteroids for } >2 \text{ weeks}$. We also deemed that lower dose steroids ($\geq 5 \text{ mg but } <20 \text{ mg}$) in conjunction with another immunosuppressive agent constituted a very high risk.

Cyclophosphamide

Cyclophosphamide is used in rheumatology as induction therapy for patients with organ-threatening autoimmune connective tissue disease (CTD) or vasculitis. Its use is associated with a significant risk of serious infection.

In light of this evidence, we decided that ongoing oral cyclophosphamide therapy or pulsed intravenous therapy within the previous 6 months would constitute a very high risk.

Biologic agents

Biologics registry data gives us robust evidence on the risk of infection in this cohort in the UK. The incidence of serious infection (SI) in patients on the British (BSRBR-RA) Registry on biologic agents averages to 5.51 cases per 100 patient years for the entire cohort (95% CI 5.29–5.71). The 30-day mortality following SI was 10.4% (95% CI 9.2–11.6%). The BSRBR-RA also
provides a wealth of data on opportunistic infections (OI) and has demonstrated no significant differences between the drug classes on the overall incidence of OI, although the rate of Pneumocystis jirovecii infection was higher with rituximab than with anti-TNF and the incidence of TB significantly lower among rituximab users than anti-TNF users. Combined data from juvenile biologic registers suggests that infections are common with single or combined treatment but corticosteroids are the most important factor influencing infection risk. Recurrent infection rates are also increased in patients on biologics, with a 14% annual risk of recurrent infection following an index event. Respiratory infections were the most frequent (44% of all events) and increasing age and polypharmacy were significant predictors of infection recurrence. There is a small but significant increase in the risk of infection in the first 6 months after starting a biologic. Risks may vary between different biologic agents: when compared with etanercept, tocilizumab appeared to have a higher risk of SI (HR 1.22, 95% CI 1.02–1.47) and certolizumab pegol a lower risk of SI (HR 0.75, 95% CI 0.58–0.97). There is also some evidence that RA patients with high biologic drug levels have a higher risk of infection, supporting the view that once in remission biologic dose tapering may lower infection risk. Registry data has shown that rituximab within the last 12 months carries a similar infection risk to anti-TNF agents. Interestingly tocilizumab (anti-IL-6) is among the agents that have been trialled for treatment of the acute respiratory syndrome associated with COVID-19 infection.

Nonetheless, in light of the available evidence the consensus view was that for the purpose of risk stratification all routinely used injectable biologics should be grouped together in terms of assessing risk.

Small molecule JAK inhibitors

A recent systematic literature review and meta-analysis of infection risk with small molecule JAK inhibitors (JAKi) in individuals with RA reviewed 21 studies, covering a total of 11,144 patients receiving baricitinib, tofacitinib or upadacitinib. They found that absolute SI rates were low but that the incidence of herpes zoster (HZ) was higher than expected at 3.23 per 100 patient years, with the risk apparently greatest in the baricitinib-exposed population, although the differences were not statistically significant. It should be remembered that these are data derived from clinical trials and, as such, do not have the power of registry-derived ‘real-world’ data. In light of the known effects upon the immune system, the consensus view was that for the purpose of risk stratification JAK inhibitors should be grouped with injectable biologics in terms of assessing risk.

Conventional disease modifying anti-rheumatic drugs (DMARDS) and infection risk

A systematic review and meta-analysis has confirmed that methotrexate is associated with a small increased relative risk of all infections in patients with RA of the order of 1.25. Leflunomide has a similar infection risk to methotrexate. Azathioprine is used for the management of vasculitis, CTDo and as a steroid sparing agent. It is associated with an increased risk of SI including CMV viraemia. Mycophenolate is commonly used in the management of CTDo, and although associated with a lower incidence of infection than cyclophosphamide or steroids does increase the incidence of SI overall. The risk for CMV viraemia is similar to that seen with azathioprine but the likelihood of tissue-invasive CMV disease is greater.

Neither sulfasalazine nor hydroxychloroquine are immunosuppressive, they do not appear to increase infection risk in rheumatic disease patients, and they may be protective against certain infections and in the case of hydroxychloroquine against COVID-19 itself. The latter is the subject of several ongoing clinical trials including the RECOVERY trial.

In light of this evidence, methotrexate, leflunomide, azathioprine and mycophenolate were felt to be contributory immunosuppressive drugs. In general rheumatology practice methotrexate and azathioprine are used at conventional doses (up to 25 mg weekly for methotrexate and 150 mg daily for azathioprine) and in most cases higher doses are a marker of severity and associated with additional medication, which would in any case move the patient into a higher risk category. We did not therefore include a dose threshold for any of these conventional disease-modifying drugs.

Neither sulfasalazine nor hydroxychloroquine were felt to lead to an increased infection risk.

Combination therapy

Concerns have been raised about the additive risk of taking more than one immunosuppressive agent.

Combination therapy with conventional and biologic disease-modifying drugs is well established in rheumatology practice, with evidence of good efficacy and little increase in adverse events. A systematic review and meta-analysis of rituximab combined with methotrexate versus methotrexate alone in the treatment of RA reviewed a total of five RCTs with 3,299 patients (rituximab combined with MTX group = 1,787, MTX only group = 1,512). They found no significant differences between the two groups in terms of the total complication rate and the infection rate. Similar reassuring results were observed when combining leflunomide with anti-TNF, abatacept or rituximab. Studies have confirmed that methotrexate–leflunomide combination therapy is safe and well tolerated in patients with refractory RA. There are no recent publications looking at the safety and efficacy of methotrexate–azathioprine and methotrexate–cyclosporin combination therapy but a Cochrane review found an increased risk of predominantly gastrointestinal adverse events in the combination groups but did not appear to show an increase in infection. The evidence suggests that combination therapy is generally well tolerated and does not significantly increase infection rates or adverse events.

Nonetheless we considered that if it did place an additional burden on the immune system and for the purposes of risk stratification, combination therapy was considered to carry a higher risk as compared to monotherapy.

Comorbidities and disease activity

Though immunosuppressive medication was an important consideration it was acknowledged that comorbidities needed to be taken into account, as it was clear that age, underlying lung disease, ischaemic heart disease, hypertension, diabetes mellitus and chronic renal failure were all associated with more serious infection with COVID-19. A rapid review of a total of 72,314 cases recorded in China as definite or probable COVID-19 reported that 81% were classified as mild (81%, ie no or mild pneumonia),
14% were severe (ie dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (ie respiratory failure, septic shock, and/or multiple organ dysfunction or failure). The overall case-fatality rate (CFR) was 2.3% (1,023 deaths across 44,672 confirmed cases). No deaths occurred in those less than 9 years, but the 70–79 years had a CFR of 8.0% and those >80 years a CFR of 14.8%. The CFR was elevated amongst those with pre-existing comorbid conditions: 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension and 5.6% for cancer.16

There was some debate among the group on the importance of disease activity. In general well-controlled patients were felt to be at lower risk, whereas those with active disease were felt to be more vulnerable. We accept, however, that there is no evidence-based rationale for this and have therefore simply left it to the assessing clinician to make a judgement call. To highlight this fact, we placed those with well controlled disease activity in the moderate risk category. There was acknowledgement that other specialties including dermatology and gastroenterology who prescribed similar biologic drugs typically used them as monotherapy. It was felt that the focus should therefore be to identify those patients on combination therapy and to also take into consideration the use of corticosteroids. Again, the need for a consensus across the medical specialities was important; ≥20 mg of prednisolone (0.5 mg/kg for children) was agreed as inferring a very high risk. These principles led to our stratification grid (Table 1), which provided a number of different treatment scenarios and also took into account other co-morbidities (including age, underlying lung disease, ischaemic heart disease, hypertension, diabetes mellitus and chronic renal failure).

It is important to highlight the timescale in which this guidance was developed. The BSR working group had their first teleconference at 3pm on 18 March 2020, subsequently held meetings with other specialties’ representatives facilitated by the RCP and produced the final document by 4pm on 22 March 2020.

The need to produce a piece of work in a very short length of time focused our attention on the task at hand. The group were recruited pragmatically and to cover a breadth of expertise. The task was coordinated by Elizabeth Price in her role as president of the BSR with support from all the authors. The RCP coordinated the work between the different specialist groups to ensure consistency in the approach taken. The work was completed by email and teleconference on time and disseminated simultaneously with the Government announcement. We acknowledge that the grid is not perfect but it was felt to offer a usable, practical guide that clinicians could follow to assess their patients.

### Reaching a consensus

Initial thoughts were that all patients on a biologic were high risk but after discussion with other medical specialities it was acknowledged that such an approach would result in numbers far in excess of the 1.5 million target number of patients to be placed in the shielding category. There was acknowledgement that such an approach would result in numbers far in excess of the 1.5 million target number of patients to be placed in the shielding category. We accept, however, that there is no evidence-based rationale for this and have therefore simply left it to the assessing clinician to make a judgement call. To highlight this fact, we placed those with well controlled disease activity in the moderate risk category.

### Table 1. COVID-19: Identifying patients for shielding in England

| Risk stratification guide | Patients to shield | Patients to self-isolate or maintain social distance at their discretion | Patients to maintain social distance |
|---------------------------|-------------------|---------------------------------------------------------------------|-----------------------------------|
| Immunosuppressive medication | Corticosteroid dose of ≥ 20 mg (0.5 mg/kg) prednisolone (or equivalent) per day for more than 4 weeks | Well-controlled patients with minimal disease activity and no comorbidities on single agent broad spectrum immunosuppressive medication, biologic/monoclonal or small molecule immunosuppressant | Single agent 5-ASA medications (eg mesalazine) |
|                           | Cyclophosphamide at any dose orally or within last 6 months IV | Well-controlled patients with minimal disease activity and no comorbidities on single agent broad spectrum immunosuppressive medication plus sulphasalazine and/or hydroxychloroquine | Single agent 6-mercaptopurine |
|                           | Corticosteroid dose of ≥ 5 mg prednisolone (or equivalent) per day for more than four weeks plus at least one other immunosuppressive medication,* biologic/monoclonal or small molecule immunosuppressant (eg JAK inhibitors)† | Well-controlled patients with minimal disease activity and no comorbidities on a single agent broad spectrum immunosuppressive medication plus sulphasalazine and/or hydroxychloroquine | Only inhaled or rectally administered immunosuppressant medication |
|                           | Any two agents among immunosuppressive medications, biologics/monoclonals or small molecule immunosuppressants with any co-morbidity§ | Well-controlled patients with minimal disease activity and no comorbidities on a single agent broad spectrum immunosuppressive medication* at standard dose (eg methotrexate up to 25 mg per week) plus single biologic (eg anti-TNF or JAKi†) | Hydroxychloroquine |

Adapted from BSR guidance.18

*Immunosuppressive medications include: azathioprine, leflunomide, methotrexate, mycophenolate (mycophenolate mofetil or mycophenolic acid), ciclosporin, cyclophosphamide, tacrolimus, sirolimus. They do NOT include hydroxychloroquine or sulphasalazine either alone or in combination.

† Biologic/monoclonal includes: rituximab within last 12 months; all anti-TNF drugs (etanercept, adalimumab, infliximab, golimumab, certolizumab and biosimilar variants of all of these); tocilizumab; abatacept; belimumab; anakinra; seukinumab; ixekizumab; ustekinumab; sarilumumab.

‡ Small molecules include: all JAK inhibitors (baricitinib, tofacitinib etc). Small molecule immunosuppressant (eg JAK inhibitors)

§ Co-morbidity includes: age >70, diabetes mellitus, any pre-existing lung disease, renal impairment, any history of ischaemic heart Disease or hypertension. Patients who have rheumatoid arthritis (RA) or interstitial lung disease (ILD) related to connective tissue disease (CTD) are at additional risk and may need to be placed in the shielding category. All patients with pulmonary hypertension are placed in the shielding category.

Note this advice applies to adults, children and young people with rheumatic disease. We do NOT advise that patients increase steroid dose if they become unwell.

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Identifying patients

Early on in the process, it was accepted that individual rheumatology patients were not going to be easily identified by NHS Digital from within centrally held data. There are several reasons for this, including the majority of rheumatology care being ambulatory, and therefore not recorded against a specific ICD code that can be interrogated in HES. Although patients on some immunosuppressant therapies were identified centrally from PCMM data, this was predominantly to support identification of patients who had undergone organ transplantation, receiving therapies including azathioprine, mycophenolate, tacrolimus and sirolimus, and did not include secondary or tertiary care prescribing.

One of the additional challenges is that DMARDs are typically prescribed by primary care and biologics and JAKi by secondary or tertiary care. The responsibility for identifying patients for shielding would therefore fall to rheumatology teams. The BSR disseminated the guidance to all its members by email and uploaded the information to its website. The extra burden on already stretched departments to identify these patients was acknowledged. Clinicians were asked to send a template letter to patients and to also advise their GP of their high-risk status.

Following initial publication of the stratification grid, it became apparent that clinicians were experiencing challenges assessing individual patient’s risk and a scoring system (Table 2) was therefore developed to assist the process. One challenge that became apparent was assessing disease activity, as for many patients it had been as long as a year since their last assessment in clinic. Disease activity had been included within our stratification grid but the scoring system alleviated the requirement of an assessment of disease activity. Following dissemination of the scoring system, it also became apparent that well-controlled disease on a single agent conferring moderate risk was underrepresented on the scoring system. A decision was made to leave this unchanged as the general population was now required to socially distance and the priority was identifying those at highest risk required to shield.

At the time the stratification guidance was published, some rheumatology teams were already facing the challenges of depleted numbers of staff and therefore patient-facing guides were developed by our patient charities so that patients could themselves assess their risk and identify whether or not they were in the shielding group.

Conclusion

The rapid production of this guidance and its development in line with CMO guidance and in consensus with other speciality groups is important to acknowledge. The final recommendations were agreed by iterative emails and teleconferences between rheumatologists with input from other relevant specialists. All involved in the process appreciated the difficult task of developing guidance when evidence about the impact of COVID-19 on our patient group is limited. Though immunosuppressive medication was an important consideration, it was recognised that age and comorbidities needed to be taken into account and it was critical that there was consistency with other specialty groups who prescribe immunosuppressive medications. Although this was initially an England-only exercise, the devolved nations quickly adopted a similar approach and are now using the BSR risk stratification guide to ensure a consistent approach. This work has thus been instrumental in identifying the most vulnerable rheumatology patients in the UK to ensure they take appropriate action to shield themselves and are able to access relevant support.

Table 2. Risk stratification of patients with autoimmune rheumatic diseases.

| Risk factor                                                                 | Score |
|-----------------------------------------------------------------------------|-------|
| Corticosteroid dose of $\geq$ 20 mg (0.5 mg/kg) prednisolone (or equivalent) per day for more than 4 weeks | 3     |
| Corticosteroid dose of $\geq$ 5 mg prednisolone but $< 20$ mg (or equivalent) per day for more than 4 weeks | 2     |
| Cyclophosphamide at any dose orally or IV within last 6 months             | 3     |
| One immunosuppressive medication,* biologic/monoclonal† or small molecule immunosuppressant‡ | 1     |
| Two or more immunosuppressive medications,* biologic/monoclonal§ or small molecule immunosuppressant¶ | 2     |
| Any one or more of these: age $> 70$, diabetes mellitus, pre-existing lung disease, renal impairment, history of ischaemic heart disease or hypertension§ | 1     |
| Hydroxychloroquine or sulfasalazine alone or in combination             | 0     |

Adapted from BSR. To be used in conjunction with BSR guidance published 22 March 2020. Score of 3 or more: patients to shield; score of 1 or less: patients to maintain social distance.

*Immunosuppressive medications include: azathioprine, leflunomide, methotrexate, mycophenolate (mycophenolate mofetil or mycophenolic acid), ciclosporin, tacrolimus, sirolimus. It does NOT include hydroxychloroquine or sulfasalazine, either alone or in combination.

†Biologic/monoclonal includes: rituximab within last 12 months; all anti-TNF drugs (etanercept, adalimumab, infliximab, golimumab, certolizumab and biosimilar variants of all of these); tocilizumab, abatacept, belimumab; anakinra; seukinumab; ixekizumab; ustekinumab; sarilumumab; canulkinumab.

§Small molecules includes: all JAK inhibitors – baricitinib, tofacitinib etc.

¶Patients who have rheumatoid arthritis (RA) or interstitial lung disease (ILD) related to connective tissue disease are at additional risk and may need to be placed in the shielding category. All patients with pulmonary hypertension are placed in the shielding category.

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COVID-19 and high-risk rheumatology patients

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