Infection, immunosuppression, and treatment of auto-immune inflammatory kidney disease

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ABSTRACT

Immunosuppressive drugs are the cornerstone of treatment of auto-immune inflammatory diseases (AIIDs) with renal involvement. However, the most commonly used drugs in this setting can increase the risk of bacterial, fungal, and viral infection, and also impair immune response following vaccination. Recommendations and evidence on strategies for infection prevention in the setting of AIIDs treatment will be reviewed.

Key-words: immunosuppression, infection, prevention

INTRODUCTION

Immunosuppressive drugs play a major role in the treatment of immune-mediated inflammatory renal diseases, as well as in renal transplantation. In the setting of auto-immune inflammatory diseases (AIIDs), infection risk is determined not only by immunosuppressive drugs, but also by physiological mechanisms such as edema, immune cell dysregulation, and urinary loss of immunoglobulins (Ig) and complement components.

Immunosuppression benefits, inflammatory disease control, and risk of infection are intimately related: immunosuppressants increase infection risk, infection treatment requires immunosuppressive therapy adjustment that could increase inflammatory activity, but infection may also be a trigger for some diseases to relapse.

Since infection is a major cause of morbidity and treatment interference, infection risk assessment and individualized preventive strategies are important.

KIDNEY DISEASE, IMMUNOSUPPRESSIVE DRUGS, AND INFECTION RISK

Patients with kidney disease requiring treatment with immunosuppression are at a higher risk of infection. A cohort study of 489 patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) treated with immunosuppression showed a cumulative incidence of infection at 1, 2, and 5 years of 51, 58, and 65%, respectively, and of severe infection of 22, 23, and 26%. A recent study of 379 AAV patients showed these patients are four times more likely to have laboratory-confirmed infections, and four times more likely to develop infections requiring hospitalization. The underlying AIID also impacts infection risk, as observed in a study comparing 872 patients with AAV and systemic lupus erythematosus (SLE), with the former showing a higher risk of hospitalization due to infection, as well as poorer outcome of infection episodes while on immunosuppressive therapy.

Commonly used drugs for glomerulonephritis treatment include corticosteroids, cyclophosphamide, rituximab, mycophenolate mofetil (MMF), and azathioprine. These drugs may be used separately, in combination regimens, or sequentially, depending on the diagnosis, clinical features, and in regard to induction or maintenance treatment stage. In some cases, plasma exchange may also be necessary.

Several studies have evaluated the risk of infection associated with different immunosuppressive regimens used to treat immune-mediated glomerulonephritis.

Methotrexate, along with belimumab and calcineurin inhibitors such as tacrolimus, may be used in AAV or lupus nephritis, but these drugs are usually not considered as first-line therapy, and therefore will not be analyzed in this review.

CYCLOPHOSPHAMIDE

The alkylating agent cyclophosphamide is one of the most immunosuppressive therapies available. During treatment, complete differential blood counts should be obtained regularly to screen for bone marrow toxicity. Cyclophosphamide should be avoided in...
neutropenic patients, unless neutropenia is perceived as being immune-mediated.

Higher cyclophosphamide doses and long treatment duration increase the risk of hematologic toxicity. Leukopenia is common and granulocytes are likely to be affected within days to a few weeks of treatment. Lymphopenia may also occur, particularly if high doses of corticosteroids are also being used. In this setting of concomitant treatment with high-dose corticosteroids, a total white blood cell count below 4000/mm³ implies underlying immunosuppression, even if the absolute neutrophil count is above 1500/mm³, since high-dose corticosteroids cause polymorphonuclear cells to demarginate. Prompt dose adjustments should be made in leucopenia or neutropenia. However, this may not be necessary in the presence of isolated lymphopenia, as long as patients are on Pneumocystis jiroveci pneumonia (PCP) prophylaxis, recommended for almost all patients on cyclophosphamide.

**RITUXIMAB**

Rituximab is a CD20-targeting monoclonal chimeric antibody, causing depletion of B cells. B cell depletion is reversible after interruption of rituximab treatment, since stem cells and earlier B cell precursors lack the CD20 antigen and can migrate from the bone marrow to secondary lymphoid tissue to reconstitute the B cell reservoir. Subsequent normalization of B cells usually takes place six to nine months later after treatment interruption.

Although rituximab is mainly a B-cell depleting agent, data from rheumatoid arthritis (RA) patients suggest treatment may also significantly decrease the number of peripheral blood T cells, particularly CD4+ cells, months later after treatment initiation. Additionally, experimental murine models also showed treatment with anti-CD20 drugs could also affect the development or establishment of CD8+ T cell responses, which are necessary for the control of intracellular infections. Clinical relevance of these findings requires further clarification.

Rituximab should be avoided in severely immunocompromised patients or when there is an active, severe infection.

B cell depletion may cause some degree of hypogammaglobulinemia, impairment on vaccine responses, as well as dysfunction in T-cell responses due to reduction in antigen-presenting cells in the setting of B cell depletion.

**ANTIMETABOLITES: MYCOPHENOLATE MOFETIL AND AZATHIOPRINE**

MMF inhibits lymphocyte proliferation through the inhibition of inosine monophosphate dehydrogenase. It is commonly used for the prevention of organ transplant rejection, and as a corticosteroid-sparing agent in the treatment of a wide range of AIIDs. Infection risk is not thoroughly characterized in MMF-treated AAIDs patients, and most of the available data regards MMF use within solid-organ transplantation. In comparison to other immunosuppressive drugs used in the treatment of AAIDs, MMF is not usually considered to significantly increase the risk of opportunistic infections. However, a recent meta-analysis on the role of MMF in AAV patients found a similar rate of infection as the one observed in cyclophosphamide-treated patients.

Azathioprine is a derivate of the purine-mimic antimetabolite thioguanine, and the prodrug of 6-mercaptopurine. Azathioprine and 6-mercaptopurine cause a reduction of circulating B and T lymphocytes, reduce immunoglobulin synthesis, diminish interleukin-2 secretion, and inhibit the intracellular signaling of T-cell costimulation through CD28-mediated pathways.

Even though infection is a common side effect of azathioprine, infection risk is still poorly characterized. Case series reports which stem from a wide range of AAIDs, including neurological, rheumatological, and gastrointestinal disorders, describe increased infection...
risk with simultaneous use of other immunosuppressive drugs, such as corticosteroids, or other immunomodulatory drugs.

Overall, infectious complications reported with the use of antimetabolites include bacterial infections, such as Listeriosis and mycobacterial infections, but also fungal and viral infections such as Herpes zoster (H2). Antimetabolites use and PML risk is addressed below.

### TUBERCULOSIS

Latent infection by *Mycobacterium tuberculosis complex* (Mtbc) is a dynamic process and the outcome of Mtbc infection represents a wide range of immune responses to infecting mycobacteria. At one end of the spectrum, there is the possibility of successful eliminating mycobacteria and at the opposite end, fierce bacterial replication may result in fulminant tuberculosis (TB) and sepsis. The outcome of this process is influenced by the net amount of immunosuppression that results from a specific AAID and its underlying immune dysfunction and/or inflammatory disease activity, on top of which treatment with immunosuppressive drugs overlaps.

Even what may be considered as low-risk immunosuppressive treatment, such as low-dose corticosteroid use, can impair the immune responses triggered by exposure to mycobacteria, hence increasing the risk of active tuberculosis. This risk rises with increasing doses of corticosteroid therapy, but even with lower doses it is still not negligible, as indicated by an odds ratio close to 3 of progressing from latent to active TB when prednisone <15 mg/day is used.

Unlike active TB, there still is no gold-standard method for the diagnosis of latent TB (LTB). National guidelines unanimously identify patients eligible for treatment of LTB as those who, after having active TB ruled out, have either a positive interferon-gamma release assay (IGRA) or tuberculin skin test (TST) result equal to or greater than 5 mm, depending on whether or not they are immunosuppressed. These are the methods currently available, only allowing for an indirect interpretation of the presence of LTB, and entirely relying on a fully complete immune response by the host after it has been exposed to Mtbc antigens. None of these methods makes it possible to distinguish between active infection and latent infection, cured or untreated TB, nor to differentiate recent exposure from past exposure.

TST result can be influenced by past vaccination with BCG, leading to false-positive results. However, impact of BCG progressively reduces over time, is scant after 15 years, and a strongly positive TST result is very unlikely attributable to prior BCG vaccination. TST false positive results may be due to previous exposure to non-tuberculosis mycobacteria. On the other hand, IGRA results have better sensitivity and specificity, but can be influenced by inflammatory activity, lymphopenia, or immunosuppressive therapies such as high-dose corticosteroids. Multiple studies have described variation in IGRA results in patients who are evaluated on several occasions, with conversions and reversal of IGRA, and the clinical outcome of these phenomenon remains to be established.

Prior to immunosuppression treatments, patients should be screened for TB. LTB treatment is considered not only according to test results, but also regarding individual risk of TB reactivation, ongoing use of immunosuppressive drugs, or predicted future need, as well as LTB treatment toxicity risk.

### CYTOMEGALOVIRUS

CMV infection in immunosuppressed patients is often severe and can be fatal. A retrospective analysis of AAV patients found that, apart from previously described risk factors such as cyclophosphamide, rituximab, and corticosteroids, severe disease and granulomatosis with polyangiitis (GPA) were independent risk factors for CMV infection. CMV infection in the setting of AAIDs is a wide theme and prevention strategies are still being debated. Whenever CMV infection or risk factors for severe CMV disease are suspected, consultation with an infectious diseases expert should be sought.

### PULMONARY PNEUMOCYSTOSIS PROPHYLAXIS

There are already guidelines recommending PCP prophylaxis for certain well-established oncology and transplantation settings. However, PCP prophylaxis in patients with AAIDs is still a gray area. Additional risk factors may exist and objective individual risk stratification is often difficult, since CD4 lymphocyte count may not reflect PCP risk in the same way it does for HIV patients. Nevertheless, it is beyond question that prevention in this setting saves lives, since PCP in non-HIV patients usually progresses with more rapid and severe symptoms, patients tend to experience worse outcomes, mortality rates range between 30-60%, and PCP diagnosis is frequently challenging.

A 2007 systematic review by Green et al. proposed that prophylactic trimethoprim-sulfamethoxazole (TMP/SMX) should be considered when the risk of PCP is above 6.2%. A 2014 review by Roux et al. provided some insight into PCP risk stratification, showing that in the setting of AAIDs with renal involvement, the most common underlying condition in PCP cases is GPA (8%-12%), followed by polymyositis nodosa (PAN) (6.5%), and that SLE accounts for 2%-3%. In a recent systematic review, according to pooled data, PCP overall incidence in GPA is 6%, and these patients account for 75% of PCP cases among AAVs.

Impaired cellular immunity due to lymphopenia and drugs may also contribute to PCP risk. Although corticosteroids are the drugs most commonly implicated as a risk, there are still some conflicting data regarding the threshold daily dose, the cumulative dose, the administration route, the underlying AAID, and whether the type of combination regimens with other immunosuppressive drugs can also impact PCP risk. Prolonged neutropenia and recurrent or active CMV infection may also increase PCP risk.

Published data regarding PCP risk and indications for prophylaxis are summarized in Table 1.

TMP/SMX is the drug most frequently used in PCP prophylaxis, either 400/80 mg once a day or double-strength tablets 800/160 mg, given three times per week. When necessary, alternatives include atovaquone, aerosolized pentamidine, or dapsone.
Table 1

Situations where PCP prophylaxis is recommended32,33,36,37,42

<table>
<thead>
<tr>
<th>In the setting of AAIDs, renal involvement, and need for immunosuppressive treatment</th>
<th>Other settings</th>
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<tbody>
<tr>
<td>• Routine prophylaxis during induction therapy of GPA</td>
<td>• Solid organ transplant recipients</td>
</tr>
<tr>
<td>• Routine prophylaxis during induction therapy of PAN</td>
<td>• Selected autologous HCT recipients</td>
</tr>
<tr>
<td>• GPA and treatment with prednisone ≥ 20 mg/d for ≥ 1 month</td>
<td>• Allogeneic HCT recipients</td>
</tr>
<tr>
<td>• AAV treated with prednisone ≥ 20 mg/d for ≥ 1 month plus cyclophosphamide or rituximab</td>
<td>• Patients with acute lymphocytic leukemia</td>
</tr>
<tr>
<td>• Connective tissue disease with renal involvement and treatment with prednisone ≥ 20 mg/d for ≥ 1 month</td>
<td>• Patients receiving alemtuzumab</td>
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<tr>
<td>• Patients receiving cyclophosphamide</td>
<td>• Patients receiving idelalisib</td>
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<tr>
<td>• Patients receiving prednisone ≥ 20 mg/d for 1 month plus a second immunosuppressive drug</td>
<td>• Patients receiving concomitant temozolomide and radiotherapy</td>
</tr>
<tr>
<td>• Patients receiving methotrexate and prednisone ≥ 20 mg/d for ≥ 1 month</td>
<td>• Patients receiving multiple chemotherapeutic agents</td>
</tr>
<tr>
<td>AAV = Antineutrophil cytoplasmic antibody-associated vasculitis; GPA = granulomatosis with polyangiitis; HCT = hematopoietic cell transplant; PAN = polyarteritis nodosa</td>
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</table>

Chemoprophylaxis should be maintained as long as immunosuppressive treatments last and during increase in dose or number of immunosuppressive drugs. In patients treated with high-dose corticosteroids and/or cyclophosphamide, PCP risk may persist after treatment discontinuation.

Available data confirms that all TMP/SMX regimens appear to be safe and are recommended for PCP prophylaxis, particularly in patients with GPA or microscopic polyangiitis (MPA). It may also be considered in SLE patients on high corticosteroid therapy36, even though TMP/SMX in SLE patients is not usually routinely recommended, due to the theoretical risk of TMP/SMX induced flare, along with the low incidence of PCP in these patients33,37.

In GPA patients, the role of TMP/SMX prophylaxis seems to be particularly beneficial. Not only is GPA the most common AIID associated with PCP, but TMP/SMX has also been used as induction treatment in GPA limited to upper and lower airways without systemic involvement33. Data from renal transplant recipients suggest MMF may have some protective effect against PCP40.

TMP/SMX may also confer some protection against community-acquired respiratory, gastrointestinal, and urinary tract infections. It has been debated whether routine use of TMP/SMX in patients on immunosuppressants could also prevent salmonellosis, infection with *Haemophilus* species and staphylococci, and depending on dosing regimens, episodes of listeriosis, nocardiosis, and legionellosis, as well41.

### IMMUNIZATIONS

Despite scarce data, there is awareness of the higher burden of vaccine-preventable diseases (VPD) in AAIDs, as confirmed by a 2019 systematic literature review43. These patients are prone to contracting influenza and influenza-related complications, pneumococcal disease, HZ, as well as having a higher prevalence of genital human papilloma virus (HPV), including high-risk serotypes. The risk of pneumococcal disease, HZ, and HPV was higher in SLE patients. These data stress the importance of preventing infection through immunization with individualized tailored strategies.

AAIDs do not seem to increase the risk for developing severe COVID-1944. However, vaccination is advised, since these patients tend to have more frequent comorbidities related to severe COVID-19 risk, such as advanced age, kidney and heart disease, pulmonary disease, hypertension, obesity, and diabetes.

Recommendations regarding vaccination are summarized in Table 2.

### HBV REACTIVATION RISK

All patients must be screened for HBV infection prior to immunosuppression. HBV-R can lead to fulminant hepatic failure and high mortality rate.

Risk stratification is a useful tool, and takes into account HBV markers, underlying disease, type and duration of immunosuppressants. Table 3 shows risk stratification and strategies.

Irrespective of the pharmacologic category of immunosuppressant that is ongoing or is predicted to be used, patients with chronic HBV infection should receive antiviral therapy. Antivirals such as tenofovir (tenofovir disoproxil fumarate or tenofovir alafenamide) or entecavir should be used in patients warranting antiviral prophylaxis or treatment, since they have higher genetic barrier. Lamivudine is no longer recommended in these settings, since it has a lower genetic barrier and it is frequent for resistant viral variants to emerge after prolonged use, typically after 6 months48,49.

Once immunosuppressive therapy is stopped, antiviral treatment should be maintained for at least 6 months, or 1248-1849 months in high-risk patients, particularly if a B-cell depleting agent such as rituximab was used. In such cases, monitoring is still warranted, since cases of late HBV-R have been described50.

Even though risk stratification is useful, in real life objective stratification may not be straightforward, transition between risk categories is frequent, and there are differences in HBV prophylaxis or preemptive therapy orientations regarding detectability of HBsAg, anti-HBs and anti-HBc.

The American Association for the Study of Liver Disease (AASLD) recommends antiviral prophylaxis in HBsAg(-), anti-HBc(+) patients receiving anti-CD20 antibody therapy as rituximab, irrespective of anti-HBs titer48. The European Association for the Study of the Liver (EASL) also recommends such strategy, specifically regarding
Table 2
Recommendations for vaccination in AIIDs (adapted from Furer et al.45 and Soy M et al.46,47)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Comment</th>
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<tbody>
<tr>
<td><strong>General immunizations</strong></td>
<td></td>
</tr>
<tr>
<td>Vaccination should preferably be administered during quiescent stage of AIIDs.</td>
<td>In patients with active disease, immunization should not be precluded and should be considered on individual basis.</td>
</tr>
<tr>
<td>Non-live vaccines can be administered during corticosteroids and DMARDs treatment.</td>
<td>Caution: live-attenuated vaccines administration, see below.</td>
</tr>
<tr>
<td>AIIDs patients should receive general immunizations according to general recommendations.</td>
<td></td>
</tr>
<tr>
<td>Patients with AIIDs should receive tetanus toxoid vaccination in accordance to general recommendations. Passive immunization should be considered for patients treated with B cell depleting therapy.</td>
<td></td>
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<tr>
<td>Patients should receive vaccinations against HPV in accordance with recommendations for the general population.</td>
<td>Female patients with SLE are at a particular high risk of genital HPV infection, including high-risk serotypes.</td>
</tr>
<tr>
<td>Immunocompetent household members of AIIDs patients should receive vaccines according to national guidelines, with the exception of the oral polio vaccine.</td>
<td>Immunocompetent individuals, who live in a household with immunosuppressed patients, should receive inactivated vaccines as well as live-attenuated vaccines such as MMR, according to national guidelines.</td>
</tr>
<tr>
<td>AIID immunosuppressed patients should be aware of transmission risk when live-attenuated oral vaccines such as rotavirus vaccines are given to infants.</td>
<td>Highly immunocompromised patients should avoid handling diapers of infants vaccinated against rotavirus for at least 4 weeks following the administration of the vaccine.</td>
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<tr>
<td>Prior to travel, patients should be evaluated by a travel medicine specialist familiar with immunosuppressive treatments and specificities related to vaccination and preventive measures in this setting.</td>
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<tr>
<td><strong>Recommendations regarding specific immunosuppressive treatments</strong></td>
<td></td>
</tr>
<tr>
<td>Vaccines should be preferably administered prior to planned immunosuppression, in particular B cell depleting therapy.</td>
<td>Necessary immunosuppressive treatment in severe cases should not be delayed and immunosuppressants should be prioritized over early administration of vaccines.</td>
</tr>
<tr>
<td>In patients on B cell-depleting therapy, vaccination should be given at least 6 months after the administration and 4 weeks before the next course of treatment.</td>
<td>When this time window is not possible, vaccination may be considered under B-cell depleting therapy, taking into account potential suboptimal response to vaccine.</td>
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<tr>
<td><strong>Recommendations regarding specific immunizations</strong></td>
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<tr>
<td>Pneumococcal vaccination should be strongly considered.</td>
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<tr>
<td>Annual influenza vaccination should be strongly considered.</td>
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<tr>
<td>Hepatitis A and/or B vaccine should be administered for non-immune patients at risk.</td>
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<tr>
<td>Herpes zoster vaccination may be considered in high-risk patients.</td>
<td>Immunization recommended for patients ≥50 years old, using:</td>
</tr>
<tr>
<td>Live-attenuated vaccines should generally be avoided in patients on immunosuppressive treatment.</td>
<td>– a live-attenuated vaccine if administration is not contra-indicated or</td>
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<tr>
<td>When necessary, live-attenuated vaccines can be given 4 weeks before immunosuppressive treatment initiation. If immunosuppressants have already been given, vaccination should take place when ≥ 4 weeks have passed since last administration.</td>
<td>– a new non-live recombinant subunit adjuvant zoster vaccine, when available.</td>
</tr>
<tr>
<td>Vaccination against yellow fever should be generally avoided in AIIDs patients on immunosuppression.</td>
<td>Definition of immunosuppressive therapy:</td>
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<tr>
<td></td>
<td>– prednisone ≥ 20 mg/day or equivalent for ≥ 2 weeks</td>
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<td></td>
<td>– methotrexate ≥ 0.4 mg/kg/week</td>
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<td></td>
<td>– azathioprine ≥ 3.0 mg/kg/day</td>
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<td>– 6-mercaptopurine ≥ 1.5 mg/kg/day</td>
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<td></td>
<td>– bDMARDs</td>
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<td></td>
<td>– tsDMARDs</td>
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<tr>
<td><strong>COVID-19 vaccination</strong></td>
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<tr>
<td>Vaccination should be preferably made when disease activity is under control and when there is no concurrent infection.</td>
<td>Ongoing immunosuppressive drugs should be carefully reviewed before vaccination.</td>
</tr>
<tr>
<td>Vaccination of patients receiving high-dose corticosteroids should be done when the daily corticosteroid dose falls below prednisone 10 mg/day or its equivalent.</td>
<td>Low-degree immunosuppression does not appear to decrease antibody responses to vaccines.</td>
</tr>
<tr>
<td>In clinically stable patients, the scheduled dose of methotrexate before the vaccination and the subsequent weekly dose may be skipped.</td>
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<tr>
<td>For patients who are receiving intravenous cyclophosphamide, cyclophosphamide should be given approximately one week after each vaccine dose, when feasible.</td>
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<tr>
<td>Ideally, vaccination should be done before the initiation of any bDMARDs.</td>
<td>A safety margin of 14 days before and after vaccination may be considered in clinically stable patients.</td>
</tr>
<tr>
<td>Patients receiving rituximab should be vaccinated at least 4 weeks before treatment or 6 months after treatment is received.</td>
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<tr>
<td>Patients who are more likely to have drug allergies such as SLE patients should be monitored for a longer period of time (up to 150 min) after vaccination.</td>
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AIID – auto-immune inflammatory disease; bDMARDs – biological disease-modifying anti-rheumatic drugs; DMARDs – disease modifying anti-rheumatic drugs; MMR – measles, mumps, and rubella vaccines; tsDMARDs – targeted synthetic disease-modifying anti-rheumatic drugs; SLE – systemic lupus erythematosus
The role for anti-HBs in screening before immunosuppressive therapy is still under debate, since its presence may not prevent HBV reactivation. Nonetheless, anti-HBs might be useful in further characterization of risk stratification, as suggested by some studies comparing HBV-R in hematological and non-hematological patients, proposing that since patients is possible through larval skin penetration after being passed on by stool, infection can persist for decades within hosts and autoinfection is possible through larvae skin penetration again after 2 weeks, which is the duration of one auto-infection cycle. Authors recommend ivermectin 200 mcg/kg daily for 2 days, performed if frequent monitoring is not possible, consider antiviral prophylaxis. Prevalence rates of Strongyloides stercoralis and Strongyloides stercoralis infection are at risk for Strongyloides stercoralis infection. Since this helminth’s life cycle can occur entirely in human hosts and autoinfection is possible through larval skin penetration after being passed on by stool, infection can persist for decades within the same host. A cross-sectional study in an endemic region found an overall prevalence of strongyloides in SLE patients of 15.6%. In a retrospective Portuguese cohort study of 415 AIDs patients screened for strongyloides, 13% had positive serology. In the setting of immunosuppression, severe disseminated infection can occur, as well as fulminant hyperinfection. Coinfection with human T-lymphotropic virus type I (HTLV-1) is also an important risk factor for severe disease, since it is associated with impaired immune response against Strongyloides and higher rates of treatment failure. Corticosteroids, cytotoxic drugs and hypogammaglobulinemia have been associated with a higher risk of strongyloides, as well as solid organ transplantation. Prior to immunosuppressants, patients should be screened for Strongyloides, preferably with serologic tests and when positive, offered preventive treatment. If immunosuppression cannot be delayed and epidemiologic exposure is relevant, preventive treatment with ivermectin should be given, pending test results. The optimal treatment regimen is uncertain, and most authors recommend ivermectin 200 mcg/kg daily for 2 days, performed again after 2 weeks, which is the duration of one autoimmune inflammatory reconstitution syndrome (IRIS).

### STRONGYLOIDIASIS

Immunosuppressed patients are at risk for Strongyloides stercoralis infection. Since this helminth’s life cycle can occur entirely in human hosts and autoinfection is possible through larval skin penetration after being passed on by stool, infection can persist for decades within the same host. A cross-sectional study in an endemic region found an overall prevalence of strongyloides in SLE patients of 15.6%. In a retrospective Portuguese cohort study of 415 AIDs patients screened for strongyloides, 13% had positive serology.

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### PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

PML is caused by reactivation of the polyomavirus JC, causing a severe demyelinating disease that can affect gray and white matter of the central nervous system, occurring almost exclusively in immunosuppressed patients. Apart from HIV-infection, PML cases have also been reported in cancer patients, particularly those with hematological diseases treated with rituximab, leading in 2007 to package inclusion of a “black box warning”.

PML has also been described in AIDs and risk seems to be mostly related to the use of immunosuppressants such as corticosteroids, cyclophosphamide and MMF, apart from rituximab. Risk stratification according to AIDs and/or immunosuppressants is difficult, and available data derives from international registries, cohort retrospective analysis and small case reports.

The FDA Adverse Event Reporting System (FAERS) database included 58 and 3 confirmed cases of PML in autoimmune and GPA/microscopic polyangiitis (MPA) rituximab-treated patients, respectively; the approximate total incidence rate ranged from 1.39-1.87 cases per 10,000

#### Table 3

<table>
<thead>
<tr>
<th>HBV-R risk and strategies (adapted from Terraul et al. and Lampertico et al.)</th>
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<tbody>
<tr>
<td><strong>Risk (%)</strong></td>
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<tr>
<td>Very high risk (&gt;20%)</td>
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<td></td>
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<tr>
<td>High risk (11-20%)</td>
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<tr>
<td>Moderate risk (1-10%)</td>
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<tr>
<td>Moderate risk (1-10%)</td>
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<tr>
<td>Low risk (&lt;1%)</td>
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<td>Very low risk</td>
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rituximab-exposed patients, including cancer patients. A 2017 review of rituximab-related PML confirmed cases in GPA/MPA patients found a very low reporting rate defined as <1 per 10,000 patients, noting that these patients frequently also receive immunosuppressant agents and high-dose corticosteroid therapies that may be additional risk factors for PML.

In a 2012 review within the FAERS database, of 34 confirmed cases of PML among patients with AIIDs, 17 had a diagnosis of SLE, suggesting that SLE patients appeared to have susceptibility to the development of PML, compared to patients with other systemic immunosuppressive treatments. This was not confirmed in a recent observational study, where, among a cohort of 7455 adult SLE patients, PML was suspected in one patient and confirmed in only one other, developing in the setting of severe lymphopenia and one year after cyclophosphamide treatment. Cyclophosphamide and PML risk were also suggested back in 2012 by Molloy et al., whose study found confirmed PML cases in 5 MMF-treated SLE patients and 12 SLE non-MMF treated patients, all of whom had been treated with other immunosuppressive agents, including cyclophosphamide. PML is also described in kidney transplant recipients treated with MMF, with a reported incidence of 14.4 cases per 100,000 person-years, although this was not statistically significant when compared with non-MMF treated patients.

PML can also develop in the setting of immune reconstitution after withdrawal of immunosuppressive therapies, as suggested by the findings that some patients present inflammatory changes on MRI, hinting at “inflammatory PML”, similarly to what is very well described in the setting of HIV infection and IRIS.

**IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME**

IRIS was first described in HIV patients after initiation of antiretroviral therapy. IRIS can present by paradoxically worsening symptoms of a previously documented infection despite ongoing treatment, or by unmasking of an until-then unknown, quiescent opportunistic disease. The advances in the treatment of AIIDs and cancer patients have allowed for IRIS cases to occur when immunosuppressive treatment is withdrawn or scaled down.

The mechanisms subjective to IRIS are still incompletely understood. Information compiled from HIV patients and animal models suggest that not only lymphopenia itself, but also failure to clear the pathogen by T cells before T cell reconstitution takes place can result in excessive priming of the innate immune system once immune recovery ensues, causing an exaggerated proinflammatory response to the opportunistic disease, due to a sudden shift from immunosuppression to immune reconstitution.

IRIS symptoms depend on the underlying opportunistic pathogen and multiple cytokines and chemokines have been pointed out to be involved in the pathophysiology, such as interleukin (IL)-6, IL-12, TNFα and interferon-γ.

The incomplete characterization of IRIS in the setting of AAIDs makes it difficult to predict, diagnose, and treat.

The very few reports of IRIS in immunosuppressed AIID patients with renal involvement include cases such as an SLE patient with non-tuberculous mycobacteria infection after previous treatment with cyclosporin, azathioprine, MMF, and leflunomide, and another SLE patient previously treated with high-dose corticosteroid, MMF, and tacrolimus who presented Strongyloides stercoralis, HTLV-1, and CMV coinfection.

A clinical trial with 180 GPA patients treated with cyclophosphamide and/or corticosteroids found that, in a group of patients who had HZ, most of them developed it after cyclophosphamide was discontinued, hinting at the possibility of underlying immune reconstitution.

## CONCLUSION

The higher infection risk observed in AIID patients and renal disease is related not only to the underlying disease, but also to the drugs most commonly used in this setting. Infection risk assessment is fundamental to define individualized tailored strategies for infection prevention, either by preventive treatment/prophylaxis or through vaccination. Close monitoring is warranted during periods of more intensive immunosuppressive treatment, but late reactivation of infection is possible and a small number of IRIS cases has emerged. Given the uncertainty in some infection prevention strategies in this setting, further risk-benefit studies are required.

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