Infectious complications in AIHA

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Autoimmune hemolytic anemia (AIHA) may be frequently challenged by infectious complications, mainly as a result of immunosuppressive treatments administered. Furthermore, infectious agents are known triggers of AIHA onset and relapse. Although being risk factors for mortality, infec-tions are an underestimated issue in AIHA.

autoimmune hemolytic anemia steroids rituximab

1. Introduction

Autoimmune hemolytic anemia (AIHA) encompasses a group of heterogeneous conditions mainly characterized by red blood cell (RBC) lysis due to autoantibodies against surface erythrocyte's antigens. Based on the thermal characteristics of the autoantibody, AIHAs can be classified into warm forms, generally caused by IgG antibodies reacting at warm temperatures and able to fix complement in some cases; cold agglutinin disease (CAD), due to IgM antibodies that agglutinate RBCs at low temperatures and lyse them via the complement cascade activation; and mixed forms (coexistence of warm and cold autoantibodies) [1][2]. Infections in AIHA are a known player in the pathogenesis of the autoimmune process. On the other hand, infections can occur also as consequence of the disease and its treatments. There is increasing awareness of infections in AIHA, as they can impact on outcome, including morbidity and fatality. Additionally, AIHA can be secondary to systemic autoimmune diseases and lymphoproliferative disorders, whose treatments may further increase the infectious risk. Likewise, AIHA is frequently observed in primary immunodeficiencies (PIDs) that are characterized by a well-known infectious diathesis. The clinical management of infections and prophylactic measures in primary AIHA remains largely unknown, at variance with secondary forms. The only available data derive mainly from retrospective series and case reports, or from more recent clinical trials with novel drugs.

2. Prevalence of Infections in Primary AIHA

In a large multicenter Italian study on 308 primary AIHAs, infectious complications were registered in 26 patients (8.4%), of whom 11 were grade 4 (according to the Common Terminology Criteria for Adverse Events) and five were fatal [3]. They consisted mostly in pneumonia, and the causative agents were Pneumocystis jirovecii, Mycoplasma pneumoniae, Staphylococcus epidermidis, Pseudomonas aeruginosa, Varicella Zoster virus (VZV), and Candida albicans. They were not associated with AIHA type and severity nor with the number of medical therapies. Notably, splenectomy was the only factor associated with severe infectious complications (grade ≥ 3). The same authors in a subsequent larger series with an extended follow-up reported a higher proportion of infections (14%), mostly in warm and mixed subtypes [4]. In another study on 33 primary AIHA patients from South

India followed for a median period of 50 months, four developed infective episodes (two pneumonias, one popliteal abscess, and one sepsis, with no isolations): one was grade 2, two were grade 4, and one resulted in a fatal sepsis. In detail, one pneumonia occurred on a very low dose of prednisone (<5 mg/day) and azathioprine (AZA), while the other complicated a cerebral vein thrombosis requiring intensive care [5]. More recently, in an Italian single-center analysis of 225 primary AIHAs, a total of 45 infections were recorded in 29 patients (up to four episodes in one patient) over a 3-year follow-up. Two third of infections were >G3 and two were fatal (post-splenectomy sepsis and Pneumocystis jiroveci pneumonia). Of note, 60% occurred during an active phase of the disease and 14% at the time of AIHA diagnosis. Patients with infectious complications also had higher rates of thrombotic events and Evans' syndrome (association with immune thrombocytopenia). Additionally, patients with infections had received more lines of therapy, particularly rituximab, splenectomy, and immunosuppressants (AZA, cyclophosphamide and cyclosporine) [6]. Focusing on fatal outcome, a study of 83 AIHA patients in the period 1980–2000 reported 13 deaths, of which five related to infective episodes [7]. A single-center French experience on 60 warm AIHAs reported two deaths, both occurring in splenectomized patients, and still on immunosuppressive therapy. In detail, the first patient had superimposed pneumococcal-related sepsis complicating a H1N1 influenza pneumonia, and the second a Gram-negative bacilli-related sepsis in a previous history of pneumocystosis and pulmonary aspergillosis [8]. In the Italian study, the occurrence of infections was strongly associated with death (hazard ratio 11.47; 95% CI 3.43–38.4, p = 0.0004). Finally, a study of 101 warm AIHA performed in Thailand indicated sepsis as the most common cause of death, supervened in 11% of patients [9]. Altogether these findings indicate that infections in AIHA occur in 6–14% of cases, and may result in fatal outcome.

3. Infectious Risk Associated with AIHA Therapies

The risk and type of infections associated with AIHA treatments differ according to the dose, the time of exposure and the depth of immunosuppression induced by each therapy. Table 1 summarizes the main findings for the different AIHA treatments, detailed separately as follows.

Table 1. Infectious risk associated with autoimmune hemolytic anemia (AIHA) treatments.

Treatment	Main Warnings	References
Corticosteroids	- Infectious risk is dose-dependent - Also prolonged use of low-dose steroids is associated with atypical and opportunistic infections	[10][11][12]
Rituximab	- Safe as single agent	[13][14][15][16][17]

	- Risk of hepatitis B virus reactivation, if antiviral prophylaxis not instituted - Risk increases in chemotherapy-combined regimens or in the context of severe immunodepression (warning for PML)	
Splenectomy	- Infections in 6–7% of AIHA patients - Encapsulated bacteria are the main pathogens isolated in OPSI, which can be fatal - Risk decreases with proper patient's education and vaccinations	[18][19]
Classic immunosuppressive agents	- CTX, MMF, and AZA are associated with increased infectious risk by several pathogens - Cyclosporine seems safer than the abovementioned drugs	[20][21][22]
Complement inhibitors	- Increased risk of encapsulated bacterial infections	[23][24]
BCR pathway antagonists	- PI3Kδ inhibitors are associated to PJP - Fostamatinib (used in RA patients) has an increased infectious risk	[25][26]
Proteasome inhibitors	- Apparently safe in AIHA	[27][28]
FcRn antagonists	- Reported to be safe in ITP patients	[29][30]

PML: progressive multifocal leukoencephalopathy, AIHA: autoimmune hemolytic anemia, OPSI: overwhelming post-splenectomy infection, CTX: cyclophosphamide, MMF: mycophenolate mofetil, AZA: azathioprine, BCR: B-cell receptor, PI3Kδ: phosphoinositide 3-kinase delta, PJP: Pneumocystis jirovecii pneumonia, RA: rheumatoid arthritis, FcRn: neonatal Fc receptor, ITP: immune thrombocytopenia.

3.1. Steroids

Steroid-associated infectious risk has been largely reported, together with other side effects (i.e., osteoporosis, diabetes mellitus, and hypertension). The mechanisms by which corticosteroids impair the immune response against pathogens are multiple, including reduced opsonization and phagocytosis of bacteria, impaired T cell function (increasing the risk for mycobacterial, viral, and fungal infection), and enhanced eosinophil apoptosis (favoring parasitic infections). In fact, several opportunistic infections have been reported, i.e., Pneumocystis jirovecii pneumonia (PJP; especially with doses >30 mg/day) [31], aspergillosis, candidiasis, strongyloidiasis, cryptococcosis, and VZV and tuberculosis (TB) reactivations [32]. A recent large study (more than 275,000 adults with various conditions) reported a significantly higher risk of infections in the steroid-exposed group. In detail, hazard risk ranged from 2.01 for cutaneous cellulitis to 5.84 for lower respiratory tract infections, and it correlated positively with steroid dose, independently of the underlying condition. In rheumatoid arthritis (RA), the increased risk of infections was attributable to steroids even at low doses (i.e., 5 mg/day or less) [33]. Moreover, a case–control study conducted on almost 12,000 over-65 RA patients found that continuous treatment with 5 mg prednisolone for the last 3 months, 6 months, or 3 years had a 30%, 46%, or 100% increased risk of serious infections, respectively, halving the risk only many months after discontinuation. Similarly, in systemic lupus erythematosus (SLE) infections are one of the leading causes of morbidity and mortality, and a dose >7.5–10 mg/day of prednisone is a well-recognized risk factor [34]. Although being the backbone therapy, no studies addressed the steroid-related infectious risk in AIHA. Retrospective data showed that primary AIHA patients experiencing infections received a mean cumulative dose of corticosteroids of 8.2 kg for a median time of 12 months before the first event. Finally, it is noteworthy the description of six cases of cryptococcal infections in AIHA treated with steroids only. One was an elderly non-HIV non-transplanted patient who developed disseminated cryptococcal disease while receiving high-dose prednisone (100 mg/day) [35]; the other five AIHA patients contracted cryptococcal meningitis while on prednisone >15 mg/day. Altogether, these data suggest that steroids represent a risk factor for infections, particularly at high doses but also at low and prolonged regimens. Moreover, they are also associated with infections caused by uncommon agents, including fungi and parasites.

3.2. Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody targeting B cells, used as single agent or combined with chemotherapy. It has proven effective both in warm and cold AIHAs, representing the preferred option at relapse in the former and the first-line treatment in the latter. Rituximab has been associated with an increased infectious risk, related to its B cell and immunoglobulin-depleting effect. A clear association is established between rituximab and progressive multifocal leukoencephalopathy (PML), mostly in hematologic malignancies and bone marrow transplantations. PML is a devastating demyelinating disease of central nervous system caused by the reactivation of John Cunningham virus (JCV), a polyomavirus that latently infects the kidneys of almost 50% of healthy adults. More uncommon infections related to rituximab are described in retrospective case series, and include PJP, enterovirus encephalitis, parvovirus B19, cytomegalovirus (CMV), West Nile virus, and babesiosis [36]. In follicular lymphoma, a meta-analysis shows that severe infections occurred when the drug is used as maintenance therapy [37]. At variance with lymphoproliferative disorders, data on systemic autoimmune disorders indicate that rituximab is not associated with a significant infectious risk. In fact, PML is only a rare complication, reported to be less than 2/100,000 patients in systemic vasculitides [38]. Moreover, only mild infections are reported in RA clinical trials [39].

Finally, a recent systematic review evaluating rituximab use in autoimmune diseases found no difference in infectious rates between rituximab- vs. non-rituximab-treated patients.

As regards AIHA, a meta-analysis including 21 studies reported an incidence of about 5% of severe infections, including one PJP. A similar incidence was found in a French retrospective study of autoimmune cytopenias associated with SLE. In this cohort severe non-opportunistic infections occurred in 4.2% patients, with an estimated incidence of 1.2 severe infections/100 patient-years [40]. In cold AIHA, rituximab showed a good safety profile, with only 3% of G1 infections reported, although one fatal pneumonia 9 months after the end of therapy was recorded [41]. The same good safety profile has been reported in a cohort of elderly AIHA patients, in which only two urinary tract infections were registered over a median 31-month follow-up period [42]. As regards the low-dose rituximab regimen (i.e., 100 mg i.v. weekly for 4 weeks), no infections were registered in a median follow-up of 15 months (range 6–35) [43]. Surprisingly, the only study reporting a higher incidence of infections is an Asian case–control study in which the infectious rate was about 35% with low-dose rituximab, comparable to the cyclophosphamide (CTX)-treated arm [44]. Infection rates rise when rituximab is combined to chemotherapy. In perspective studies, Berentsen et al. reported an infection rate of 11% for bendamustine association and up to 59% when associated to fludarabine, including two fatal pneumonias [45][46]. Finally, no published data exist about PML incidence in AIHA, although this complication should be always considered in immunocompromised subjects. Taken together, these results suggest that rituximab as single agent is safe in AIHA, although associations with chemotherapy deserve higher attention.

3.3. Splenectomy

Splenectomy shows response rates similar to rituximab in warm AIHA, although long-term outcomes are poorly known; it is not effective in CAD, where extravascular hemolysis occurs mainly in the liver. lenectomy exposes patients to an increased risk of infections along with thrombotic events. For all these reasons, it is usually deferred after other second-line medical therapies; nonetheless, it still represents an option in multi-refractory warm AIHAs. A literature review for the period 1966–1996, including 6942 splenectomised patients for different reasons, found an infectious crude rate of 3% [47]. More recently, in a Danish nationwide analysis of about 4000 splenectomised patients [48] the overall incidence of infections was 7.7/100 patient-years vs. 2/100 for the general population. Finally, a multicenter analysis of 233 splenectomised immune thrombocytopenic (ITP) patients [49] reported a total number of 159 infections (two of them fatal) in 31% of patients. The main threat in asplenic patients consists of encapsulated bacteria, whose phagocytosis is impaired in the absence of splenic macrophages. In a large study including 349 septic episodes in asplenic patients, Streptococcus pneumonia was responsible for 57% of infections and 59% of deaths; Haemophilus influenzae for 6% of infections, with a mortality rate of 32%; and Neisseria meningitidis caused 3.7% of events. A particularly harmful event is overwhelming post-splenectomy infection (OPSI), i.e., a fulminating sepsis, meningitis, or pneumonia caused by encapsulated bacteria. It occurs more commonly within the first two years (range: 1 week to 20 years) and may rapidly evolve in few hours to death, if not adequately and timely treated. The mortality rate ranges from 10 to 70%, despite adequate treatment [50]. OPSI incidence and mortality greatly depend on age (more common in children <2 years old) and on the underlying disease, being higher in hematological disorders. Finally, malaria and babesiosis may be more severe in asplenic

patients, who lack the physiologic filter of the infected erythrocytes. Other microorganisms reported include Ehrlichia, Bacteroides, Enterococcus, Salmonella, and Bartonella [51]. The risk was generally higher in children and hereditary anemias, namely, thalassemia and sickle cell disease, while the lowest risk was observed in ITP patients.

Concerning AIHA, a systematic review including four studies and 48 splenectomised patients, found a post-operative infection rate of 6%, although data of long-term follow-up were missing [52]. Similarly, a more recent study on more than 4500 AIHA patients reported an incidence of 6.7% of sepsis in splenectomised subjects, including the late post-operative period [19]. Finally, some authors indicate splenectomy as a safe option if infections are adequately and promptly treated. In fact, in a series of 255 hematologic patients no cases of splenectomy-related sepsis occurred during a median follow-up of 35 months [53].

3.4. Immunosuppressive Agents

Immunosuppressive drugs are all associated with an intrinsic infectious risk, generally attributable to bone marrow toxicity. A systematic review and network metanalysis in lupus nephritis, including a total of 32 randomized clinical trials with 2611 patients, found that CTX, both low- and high-dose, mycophenolate mofetil (MMF), and AZA were associated with significantly higher risk compared to tacrolimus. For CTX, an incidence of infections (bacterial, fungal, viral, protozoal, and parasitic) ranging from 15 to 34% has been described [54]. Notably, AZA and MMF have been associated with atypical pathogens like Listeria monocytogenes and Mycobacterium species [55][56], fungal (Cryptococcus neoformans, Aspergillus, Mucor, and Pneumocystis jirovecii) and parasitic infections (Toxoplasma gondii) [57][58]. Moreover, polyomavirus (BK virus and JCV) infections have been reported with these two drugs. Conversely, the incidence of infections in autoimmune patients treated with cyclosporine A (CSA) is reported as low as 1% in clinical trials, and viral reactivation are rare. Regarding AIHA, CTX toxicity is well described, also at low doses (1–2 mg/kg/day), with bacterial pneumonia being the most common infection. The infectious risk related to CSA, MMF, and AZA in AIHA is less known since their use in this setting is described mostly as case series [59][60][61]. Taken together, these data indicate that treatment with classic immunosuppressants, especially CTX, is burdened by a relevant infectious risk, often characterized by atypical and opportunistic pathogens.

3.5. New Target Drugs

The progressive availability of new target therapies has involved also AIHA in the last years. Their infectious risk is less clear, and data derive mainly from use in diseases other than AIHA.

Upstream complement inhibitors, targeting C1s, C1q, and C3, are under investigation in cold and warm AIHAs, and the C5-inhibitor eculizumab has been used with some efficacy in CAD. These drugs cause an increased susceptibility to infections, due to the impaired opsonisation and lysis of capsulated microorganisms. Particularly, in eculizumab-treated patients with paroxysmal nocturnal hemoglobinuria there is a warning for Neisseria meningitidis infections. Data from 10-year pharmacovigilance reported 76 cases of meningococcal infections (0.25/100 patient-years), eight of which fatal. With the strict adoption of vaccination policies, the meningococcal infection rate has

been decreasing over time, but mortality remains considerable. In addition, a recent study demonstrated that continuous C5 blocking impairs IgG-mediated complement activation, suggesting that even patients receiving adequate vaccinations against Neisseria meningitidis may not be sufficiently protected [62]. Eculizumab has been also rarely associated with pneumonia, cellulitis, bacteremia, and urinary tract infections, due to Staphylococcus, Klebsiella oxytoca, Escherichia hermannii, viruses, and fungi [63]. The infectious risk associated with new complement inhibitors appears very low [64], most probably due to the extended vaccination policies required for enrollment. As a general comment, C1s- and C1q-inhibitors block only the classical complement pathway, leaving the alterative and the lectin ones intact, while C3 inhibition may impair complement activity more profoundly.

A new treatment option for AIHA is targeting the B cell receptor signaling with drugs successfully used in chronic lymphocytic leukemia (CLL) and other lymphoproliferative disorders, such as Bruton tyrosine kinase (BTK) and phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitors [65][66]. Ibrutinib use in lymphoproliferative diseases is associated with increased risk of bacterial and fungal infections, up to 40% in clinical trials and real-life experience [67]. Parsaclisib, a next-generation and highly selective PI3Kδ inhibitor, has shown to be effective in a phase 1–2 trial in relapsed/refractory B-cell malignancies, and a clinical trial in AIHA is ongoing at the time of writing (NCT03538041). It has the same mechanism of action as idelalisib, which has been associated with severe infectious complications in CLL patients, particularly PJP. However, only three septic episodes in a cohort of 72 lymphoma patients treated with parsaclisib have been registered [68]. Fostamatinib, a spleen tyrosine kinase inhibitor proven effective in RA and ITP, is under study in relapsed AIHA (NCT03764618). In a meta-analysis of patients with RA a 20% increase in infectious risk has been reported. Conversely, studies in ITP patients did not report infectious events [69].

Proteasome inhibitors such as bortezomib have also been used in AIHA with a good safety profile, at variance with the warnings reported for multiple myeloma [70].

Finally, targeting the neonatal Fc receptor (FcRn) is showing promising results in autoantibody-mediated diseases, including ITP. FcRn rescues immunoglobulins (Ig) G from lysosomal degradation, prolonging antibody's (and autoantibody's) half-life. Its inhibition has a therapeutic effect by reducing the pathogenic autoantibodies. However, it causes also the reduction of other protective immunoglobulins, resulting in hypogammaglobulinemia, although not associated with clinically relevant infections.

Taken together, data about new target therapies in AIHA show an overall good safety profile, even though each drug carries a specific spectrum of possible related infections.

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