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Sex-oriented perspectives in immunopharmacology

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ABSTRACT

Several immunopharmacological agents are effective in the treatment of cancer and immune-mediated conditions, with a favorable impact on life expectancy and clinical outcomes for a large number of patients. Nevertheless, response variation and undesirable effects of these drugs represent major issues, and overall efficacy remains unpredictable. Males and females show a distinct difference in immune system responses, with females generally mounting stronger responses to a variety of stimuli. Therefore, exploring sex differences in the efficacy and safety of immunopharmacological agents would strengthen the practice of precision medicine. As a pharmacological target highlight, programmed cell death 1 ligand 1 (PD-L1) is the first functionally characterized ligand of the coinhibitory programmed death receptor 1 (PD-1). The PD-L1/PD-1 crosstalk plays an important role in the immune response and is relevant in cancer, infectious and autoimmune disease. Sex differences in the response to immune checkpoint inhibitors are well documented, with male patients responding better than female patients. Similarly, higher efficacy of and adherence to tumor necrosis factor inhibitors in chronic inflammatory conditions including rheumatoid arthritis and Crohn's disease have been reported in male patients. The pharmacological basis of sex-specific responses to immune system modulating drugs is actively investigated in other settings such as stroke and type 1 diabetes. Advances in therapeutics targeting the endothelium could soon be wielded against autoimmunity and metabolic disorders. Based on the established sexual dimorphism in immune-related pathophysiology and disease presentation, sex-specific immunopharmacological protocols should be integrated into clinical guidelines.

1. Introduction

Immunomodulatory drugs are employed to control disease progression through manipulation of host immune responses. These agents have become a mainstay of treatment in cancer and autoimmune/chronic inflammatory diseases. Particularly in the field of cancer, the revolutionary concept of targeting immune cells rather than cancer cells has achieved unexpected success, so that nowadays immunotherapy represents the last frontier in the fight against some cancers. Since the approval of the first innovative drugs, a number of immunopharmacological approaches, differing in their targets and mechanisms of action, have been developed with the aim of enhancing or turning off the host immune response [1,2]. Among immune enhancing drugs, immune checkpoint inhibitors (ICI) have now been approved for a wide range of malignancies including metastatic melanoma, lung, renal and urothelial cancers [3,4]. These agents target inhibitory molecules and their ligands on T lymphocytes and innate immune cells within the immunosuppressive tumor microenvironment (TME), thereby unleashing these cells to recognize and kill tumors. More recently, personalized T cell-based immune enhancing therapies such as

Abbreviations: CNS, central nervous system; IBD, inflammatory bowel diseases; ICI, immune checkpoint inhibitors; IL, interleukin; MS, multiple sclerosis; NSAIDs, non-steroidal anti-inflammatory drugs; PARP, poly (ADP-ribose) polymerase; PD-1, programmed death receptor 1; PD-L1, programmed cell death 1 ligand 1; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; TME, tumor microenvironment; TNFi, tumor necrosis factor inhibitors; VEGF, vascular endothelial growth factor.

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chimeric antigen receptor (CAR)-T cell therapies have been approved for hematological malignancies, and novel next-generation adoptive therapies based on engineering of regulatory T lymphocytes and innate immune cells are under investigation [5].

Conversely, excessive activation of immune system and release of inflammatory mediators, as well as immune cell reactivity against "self" antigens, drive and sustain autoimmune and chronic inflammatory disorders and can affect other types of malignancies. Immunopharmacological strategies aimed at blocking immune cell activation have thus been exploited in these settings. Tumor necrosis factor inhibitors (TNFi), the prototype cytokine blocking drugs, antagonize TNF-α, a proinflammatory cytokine involved in the pathophysiology of multiple disease conditions, and paved the way for drugs specifically blocking other cytokines. These drugs revolutionized the treatment of rheumatoid arthritis (RA) and other systemic autoimmune disorders including ankylosing spondylitis, psoriatic arthritis (PsA) and inflammatory bowel diseases (IBD) [6].

Altogether, these pharmacological approaches are valuable treatment options, and have impacted the life expectancy and clinical outcome of a large number of patients. Nevertheless, nonresponsiveness and undesired side effects of these drugs represent major issues, and overall efficacy still remains unpredictable. Several factors have been found or postulated to affect the efficacy of immunotherapies in both cancer and inflammatory disease settings. Besides disease-intrinsic features, such as tumor cell mutational burden or local microenvironment signatures, sex/gender, microbiome and environmental/sociological factors can play a role in immunotherapy outcomes [7].

The recognition of sex importance in immunotherapy outcomes is relatively recent. Despite the obvious biological, physiological and behavioral differences between women and men, and extensive literature on the potential role played by sex in influencing drug pharmacokinetics, pharmacodynamics and activity, new therapeutic approaches are rarely tested taking sex into account. Sex-based differences in the incidence rates and prognosis of both cancer and autoimmune/inflammatory diseases have been reported. Women generally mount stronger immune responses and are more prone to chronic inflammation and autoimmunity, while exhibiting lower incidence and mortality for the majority of cancers as compared to men [8]. Sex is known to affect immune responses throughout lifetime by regulating the extent of immune cell activation, co-stimulatory/inhibitory molecule expression and inflammatory mediator release. Regulatory effects can vary based on the reproductive status and sex hormone type and levels [8]. Estrogen and androgen receptors are expressed by almost all innate and adaptive cell populations, with different isoforms associated with different lineages or cell differentiation status, leading to direct effects of their ligands on immune cell functions [9]. For instance, sex differences have been reported in the density and morphology of microglia in selected brain areas [10,11]. Notably, stroke shapes sexually dimorphic microglial phenotypes and neuroinflammatory responses that are affected by both sex chromosomes and hormones [12]. In particular, female microglia have higher expression of genes related with cell plasticity, control of inflammation and brain repair, which could contribute to neuroprotection. These genes and pathways may represent novel pharmacological targets, as discussed in Section 5 below.

Sex dimorphism in immune response probably reflects complex interactions among genes, hormones, environment and commensal microorganisms. The existence of a sex hormone-gut microbiome axis, resulting in sex differences in microbiome composition/richness, can further influence the individual response to immunopharmacological treatments [13]. Indeed, the contribution of microbiome to the efficacy of ICIs and TNFi is starting to be unraveled [14–17]. Thus, further elucidating the role of gender/sex in the regulation of the multiple interactions among immunopharmacological drugs, commensal flora and host immune response could offer opportunities to personalize treatment and enhance effectiveness in both women and men.

Emerging evidence supports the contribution of other sex/gender related factors to immunotherapy outcomes. Sociological factors and lifestyle, including diet, physical exercise, smoking and alcohol consumption, as well as use of non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics, were all reported to modulate the response to ICIs and other immunotherapies, although additional studies are needed to come to conclusive evidence [18]. Notably, all these factors are known regulators of immune responses and microbiome, and lifestyle choices are deeply influenced by gender-related psychological and socio-cultural factors. In this regard, women are reported to be more prone to follow healthier diets and eating behaviors or use less NSAIDs and antibiotics as compared to men, whereas men tend to exercise more [19].

Despite a growing body of evidence pointing to sex- and gender-based differences in immune response, studies exploring the interaction between patient's sex and efficacy of immunopharmacological agents are scarce. In this review, we will focus primarily on preclinical and clinical data related to ICIs and TNFi. We will also discuss current evidence on other immune system-modulating drugs and touch on emerging areas such as stroke, diabetes and the vascular endothelium. An overview of most relevant drugs, targets, settings and sex-related outcomes is provided in Table 1.

2. Selected studies, inclusion and exclusion criteria

The main international databases including MEDLINE, Scopus, Clarivate Analytics Web of Science and the Cochrane Library were searched for published preclinical and clinical immunopharmacological studies in relevant therapeutic areas as detailed in the following sections. Publications in English were exclusively considered. Despite the large number of reports, and although both male and female individuals were generally considered eligible for clinical studies, gender-specific analyses in terms of differences in drug efficacy and safety were seldom foreseen. Thus, the main focus of this review article was on sex-disaggregated data regarding efficacy and safety of medications, where available.

3. Cancer immunotherapy and the PD-1/PD-L1 checkpoint pathway

T lymphocytes are the main effector cells in specific anti-cancer responses, and have become a central target to manipulate immune response against cancer, although macrophages, neutrophils and innate lymphocytes also strongly contribute to tumor surveillance and killing [20]. Immune checkpoints and their ligands, key molecules in the maintenance of peripheral tolerance, are overexpressed by all these cell types in the TME and are co-employed by cancer cells to escape immune surveillance. Programmed cell death 1 ligand 1 (PD-L1) is expressed constitutively on both antigen-presenting and non-hematopoietic cells (cancer and endothelial cells), and is up-regulated by inflammatory stimuli [4].

An array of cancer therapies is available within the clinical domain, particularly in the emerging field of immunotherapy. Inhibition of the PD-L1/PD-1 interaction has become a major clinical strategy against a number of solid malignancies. The success of immune checkpoint blockade adds a new therapeutic category to the cancer therapy repertoire. However, despite efforts made on cancer cell and immune cell interaction, how cancer cells initiate immune escape is less understood. A durable response to ICIs is obtained in a minority of patients, due in part to an incomplete understanding of the regulatory processes controlling PD-L1 expression in the TME. The TME consists of various support cells subverted by the cancer cells to assist in tumor progression. Thus, expanding our knowledge of these mechanisms will serve to not only enhance current anti-PD-L1/PD-1 clinical protocols but also potentially identify novel approaches [21]. Rewiring T cells to enhance immunotherapy efficacy remains a major challenge. In fact, although ICIs enhance tumor-specific T-cell attack, they may also enhance

Table 1
Evidence levels of sex-specific responses to immunopharmacological agents.

Inervention	Pharmacological target	Sex-specific response	Setting	Refs
Immune checkpoint inhibitors (e.g. nivolumab, pembrolizumab)	programmed cell death 1 (CD279) (PD-1) / programmed cell death 1 ligand 1 (PD-L1)	Improved survival in males Renal immune-related toxicity more frequent in males	Clinical	[24,25,27,28]
TNF inhibitors (e.g. adalimumab, etanercept)	Tumor necrosis factor, membrane form and shed form	Higher efficacy and adherence in males More frequent serious infections in males, more frequent toxic liver disease and lupus-like syndrome in women	Clinical, observational	[33,44,47,48,49,50,51,53,56, 57,58,59,60,61,67,69,70,71,72, 73,74,77,78,85,86,87,88,89]
Rituximab	CD20 (membrane-spanning 4-domains, subfamily A, member 1)	Lower efficacy in women	Observational	[34,35,36,37,38,39]
Estrogens	Estrogen receptor (ER)-α and β, G protein-coupled estrogen receptor	Improved stroke outcome and skewing to resolving phenotypes in microglia	Experimental	[117]
PARP inhibitors (e.g. minocycline)	Poly (ADP-ribose) polymerase	Improved neurological outcomes in males	Experimental, clinical	[124,125]
Histamine receptor antagonists	H1-H4 receptors	Enhanced tissue responses to histamine in females	Experimental	[138,139,140,141]
Glucocorticoids	Glucocorticoid receptor (GR)	Sex-specific gene expression patterns in response to synthetic glucocorticoids Stronger functional hepatic inflammatory response in response to TLR activation by LPS in females	Experimental	[143,144]
Teplizumab	CD3e (CD3 epsilon subunit of T-cell receptor complex)	Delayed diagnosis of type 1 diabetes in high-risk females	Clinical	[153]

self-reactive T cells, leading to a variety of immune-related adverse events [22].

Immune genes are located mostly on X chromosome [8]. Accordingly, patients' sex affects the efficacy and toxicity of ICIs in solid tumors [23]. A metanalysis has shown improved survival of male versus female patients upon treatment with ICIs, consistent across patient subgroups [24]. The mechanisms of such sexual dimorphism have been explored. Sex differences have been detected in intratumor infiltrates of immune cells including activated dendritic cells, CD4+ and CD8+ effector T cells, memory CD4+ T cells that are enriched in females, whereas Th2-cells are more abundant in males [25]. T-cell dysfunction status is greater in females, whereas factors that exclude T cell infiltration into tumors (excluded phenotype) leading to immune system evasion [26] are more frequent in males [25]. Immune checkpoint expression is increased in tumor samples and exhausted in TME from female patients [25]. According to a recent report, renal immune-related toxicity was only detected in male patients receiving ICI therapy [27]. By contrast, females appear to be at increased risk of ICI myocarditis, although this has not been consistently demonstrated [28]. Thus, immunotherapy using ICIs has revolutionized the treatment landscape in oncology, but significant challenges remain. Without reliable tools to identify likely responders, patients who may have responded are not prescribed ICIs. Therefore, identification of sex-specific biomarkers should be a priority in this setting.

4. Biological drugs in immune-mediated diseases

It is known that 80% of autoimmune diseases occur in women [8]. Specific biologic agents against cytokines and lymphocytes have been developed and approved for treatment of immune-mediated diseases [29,30]. Within this large class, the most frequently used agents are TNFi including the monoclonal antibodies (mAb) adalimumab, infliximab, golimumab; the soluble TNF receptor IgG Fc fusion protein etanercept; the pegylated antibody fragment certolizumab; and a number of TNFi biosimilars. Other cytokine inhibitors include the interleukin (IL)− 6 receptor antagonists tocilizumab and sarilumab; the IL-1 receptor antagonist anakinra; the anti-IL-17A mAb secukinumab; and the anti-IL-12/IL-23 mAb ustekinumab. In particular, current biologics targeting IL-17A/F exist for the treatment of various immune-mediated inflammatory diseases, especially IL-17 F plays an important role in psoriasis disease. Bimekizumab is a rat-derived humanized mAb that simultaneously targets IL-17A and IL-17 F (dual antagonist) effective as a treatment for psoriasis [31], which has been approved by the EMA in 2021. Notably, a recent Cochrane review comparing biopharmaceuticals for plaque psoriasis identified bimekizumab as an effective drug when compared to placebo, calling for more randomized trials directly comparing active agents and including systematic sex-specific analyses [32]. Rituximab, targeting CD20 expressed on B-lymphocytes, is effective in those autoimmune diseases characterized by the presence of pathogenic autoantibodies.

Except for TNFi, limited and inconclusive data are reported regarding sex differences in the efficacy and safety of biological drugs in immune-mediated diseases. Generally speaking, adherence to biological therapies seems to be superior in men than in women, and the most common explanation for treatment withdrawal is the occurrence of adverse reactions [33]. Regarding rituximab, influence of sex and gender (if any) on efficacy and safety is not supported by clinical trial data [34-38]. Interestingly, the British Society for Rheumatology Biologics Register reported that female sex is associated with poorer efficacy of rituximab in women [36]. By contrast, the Autoimmunity and Rituximab registry, a French national registry, showed no significant sex differences in terms of EULAR response in patients with RA treated with rituximab, except that men had a higher remission rate than women after 12 months [39].

4.1. Tumor necrosis factor inhibitors

TNFi are used worldwide to treat autoimmune diseases such as RA, spondyloarthritis (SpA), including axial spondyloarthritis (axSpA) and PsA, as well as IBD, i.e., Crohn's disease and ulcerative colitis. TNFi show better efficacy and safety in men than in women [40]. Among factors underlying such sex disparity, PBMCs and neutrophils from males produce more TNF than those from females [41–43], and male patients with SpA have higher levels of circulating TNF than females [44]. TNFi have been observed to have a longer half-life in men [45]. Notably, in the synovia, androgens are able to enhance the effect of TNFi [46]. Regarding safety, men experience serious infections as side effects of TNFi more often than women [47]. On the other hand, TNFi side effects more frequently observed in women are toxic liver disease and lupus-like syndrome [48]. Moreover, women with IBD and pediatric Crohn's disease could have adverse reactions to TNFi more frequently than men [49–53].

4.1.1. TNFi in rheumatoid arthritis

RA is one of the most prevalent chronic inflammatory diseases. It primarily involves the joints, but should be considered a syndrome that includes extra-articular manifestations, such as rheumatoid nodules, pulmonary involvement, skin vasculitis, and systemic comorbidities. In developed countries, the prevalence of RA is 0.5–1.0%, with a female-to-male ratio of 3:1. The reason for this gender imbalance is not clear, but both genetic and hormonal factors are thought to be involved. In most studies focusing on the relationship between gender and RA, women were found to have higher disease activity scores, more pain and greater loss of function than men, in both early and established disease [53,54].

The introduction of TNFi has dramatically improved the outlook for RA patients. Nevertheless, about 30–40% of patients fail to respond to TNFi. In the time frame from therapy initiation until response assessment, usually 10–16 weeks later, non-responding patients suffer from uncontrolled disease with possible joint damage and potential harmful adverse effects. Sex differences in treatment responses to TNFi have been reported by retrospective studies, with males responding better than females, at least in early RA. In particular, several cohort studies in various countries in Europe and North America disclose lower remission rates for females than males who are on TNFi [55–58]. Indeed, male gender represents an independent predictor of sustained clinical remission in early RA patients on TNFi treatment [58]. Conversely, a Swedish study observed that female gender is associated with an increased risk of TNFi treatment failure [59]. In a Canadian cohort study, female RA patients reported more fatigue, worse function, and had higher disease scores than males while receiving TNFi [60]. In a meta-analysis of nearly 100 studies from several countries, female gender was an independent risk factor associated with discontinuation of biologic therapies for RA [61].

4.2. TNFi in spondyloarthritis and inflammatory bowel disease

SpA and IBD are chronic inflammatory conditions in which TNF plays a crucial pathogenic role. In SpA, TNFα level is augmented in synovia and sacroiliac joints, with concomitant bone damage and synovitis [62,63]. In IBD, increased TNF levels are observed in colonic tissue serum and intestinal lamina propria [64,65]. The pathogenic role of TNF is connected to its capability to directly damage intestinal epithelium and to affect T regulatory lymphocytes and regulatory macrophages [66].

Introduction of TNFi has significantly upgraded the management of these chronic inflammatory diseases. However, about 30% of patients are nonresponders or lose their initial response to TNFi over time. Moreover, some patients have to withdraw TNFi treatment because of severe side and/or adverse events [67,68]. Interestingly, both SpA and IBD are endowed with significant sex differences in onset, progression and response to therapy [44,69,70]. Sex differences in response to TNFi have recently been suggested, with males responding better than females [44,69,71–73]. Of note, females are less prone than males to adhere to TNFi therapy for SpA, the reasons of withdrawal being mostly lack of efficacy and onset of adverse events [74].

4.2.1. TNFi in axial spondyloarthritis

AxSpA is a chronic inflammatory rheumatic disease that mainly affects the sacroiliac joints and spine [75]. Differences in the presentation between male and female patients have been reported [76]. Male patients have greater structural damage than females, whereas female patients have a higher disease burden, longer diagnostic delays, higher disease activity and lower efficacy of treatment. In particular, female patients tend to have less adherence and lower response to treatment. Additionally, female patients with axSpA have been reported to experience lower response rates to treatment and lower disease remission when treated with TNFi [73,77,78]. Moreover, female patients tend to switch TNFi more frequently than males [78]. Of note, male patients with axSpA have been observed to produce higher levels of TNF and IL-17A than females, which could be associated with different treatment responses [79].

4.3. TNFi in psoriatic arthritis

PsA is an inflammatory musculoskeletal disease which can lead to significant joint damage [80,81]. PsA affects males and females similarly, but varies in terms of clinical manifestations, disease course and response to therapy. Female patients have higher disease activity at presentation and report greater loss of function and affected health-related quality of life in comparison with male patients [82–84]. In patients with PsA, response to therapies also differs according to demographic factors, comorbidities and previous therapies. Sex/gender differences are important determinants of response to therapy. Several observational studies in patients with PsA initiating TNFi therapies reported less favorable outcomes among female patients in comparison with male patients [85–87]. Female patients are more likely to discontinue treatment because of lower therapeutic efficacy and adverse events [88,89].

5. Therapeutic opportunities directed against microglia in neuroinflammation

Neuroinflammation is deeply involved in the pathogenesis and progression of neurological diseases. The inflammatory response in the central nervous system (CNS) is mainly driven by the resident macrophage population, named microglia, whose cell density, reactivity and phenotype widely differ among the two sexes and in different pathological conditions, opening the possibility for developing tailored pharmacological interventions for neuroinflammatory pathologies.

Microglia are resident macrophages of the CNS, where they self-renew from local precursors and differentiate into long-lived cells. Beyond safeguarding the CNS territory from microbial infections, microglia directly regulate neural cells fate and activity and maintain tissue homeostasis, through the phagocytosis of toxic material, such as aggregated proteins or invading cells [90]. As innate immune cells, microglia are endowed with a highly reactive phenotype, as they have the ability to recognize and adapt to a wide range of molecular patterns that leads to morphological re-shape, immune-metabolic reprogramming and production of a variety of signals, including cytotoxic molecules, pro- and anti-inflammatory cytokines and neurotrophic factors.

The wide range of microglia functions and the vast array of specific clues produced locally across different CNS regions lead to postulate the existence of different microglia subsets devoted to specific tasks [91]. Recent methodologies, such as single-cell analytical techniques, indeed confirmed that different subsets of microglia concomitantly exist in the CNS, characterized by genomic traits and epigenetic signatures that trigger specific phenotypes and have unique spatiotemporal distribution in the CNS [92,93].

Microglial defects can cause or support neurodegeneration and neurological diseases in humans, as demonstrated by the observation that mutations in macrophage proliferative pathways, loss of homeostatic function or gain of aberrant properties lead to neural dysfunction and neurodegeneration [94]. Single-cell transcriptomic analyses helped in identifying genes specifically (dys)-regulated in microglia from patients or animal models of neurologic diseases, including Alzheimer's disease, Parkinson's disease, epilepsy, brain metastasis and schizophrenia [93,95–98]. The relevance of these inflammatory genes as candidate disease markers is further supported by genome-wide association studies that linked these genes with increased risk for selected neurologic conditions. Therefore, recent scientific advances and technical improvements wide opened the possibility to target a specific microglia phenotype, possibly within a defined CNS region, according to the type of neurologic disease.

5.1. Sex-related differences in microglia and inflammatory neuropathology

Preclinical studies have indicated sex differences in the density and morphology of microglia in selected brain areas [10,11]. For instance, the preoptic area shows more ameboid-like microglia in male rodents and the hippocampus, whereas a higher number of phagocytic microglia is observed in females [99]. Moreover, male microglia display higher migratory ability in vitro [100], while microglia depletion during embryogenesis has more pronounced consequences on anxiolytic-like behaviors in adult female mice [101]. Bulk transcriptomic and proteomic profiles performed in microglia obtained from different experimental models revealed a number of differentially expressed genes in brain areas of the two sexes, overall pointing to male microglia being more prone to pro-inflammatory activation and female microglia showing higher expression of genes associated with cell development and morphogenesis [102,103].

The sexual dimorphism of microglia arises during the perinatal period, as a consequence of the estrogen surge occurring in males when testosterone is synthesized and converted to estrogens by the male gonads. In rodents, exposure of male brains to estrogens during neurodevelopment results in an increased number of microglia which, through the production of prostaglandin E2, trigger neuronal adaptations allowing the masculinization of brain and behavior [104,105]. Importantly, sexual differences of microglia during neurodevelopment have been associated with different predisposition to neurological pathologies, with higher incidence of neurodevelopmental diseases in males and higher dominance of neuroinflammatory conditions, such as multiple sclerosis (MS), in females [106]. Studies on the molecular mechanisms proposed the involvement of estrogen receptors and downstream pathways, which are amenable to pharmacological modulation also by approved drugs [107–109].

5.2. Influence of microglia and its sexual dimorphism on neuroinflammation and neuropathology: stroke

Neurologic diseases generally show sex-related differences in risk, severity and outcome, as well as immune components [110,111]. Since the appreciation of neuroinflammation being sexually dimorphic and strongly linked to the etiology of neurological diseases, renewed pharmacological interest began focusing on the biochemical and molecular mechanisms of the brain region, neuronal circuitry, sex and disease-specific features of microglia, in order to optimize interventions that improve therapeutic outcomes by targeting inflammation.

Post-ischemic neuroinflammation is mainly driven by microglia and plays a critical role in stroke outcome [112]. The neuroinflammatory response is observed soon after the ischemic insult and is associated with migration and activation of microglia around the infarcted area, infiltration of peripheral immune cells, disruption of the blood brain barrier, impairment of tissue reperfusion and activation of platelet adhesion, microvascular coagulation and complement-mediated brain injury. During the acute post-ischemic phase, microglia acts to limit neurotoxicity, as widely supported by experimental models and pharmacological tools that deplete microglia [113,114]. This is followed by activation of distinct molecular mechanisms (and, therefore, potential pharmacological targets) inducing a pro-resolution phenotype that counteracts inflammation and enhances tissue repair [115]. However, acute inflammation and microglia activation may persist and transform into chronic, non-resolving inflammation that critically controls neurological recovery after stroke [116].

Several studies have shown that stroke induces divergent microglial phenotypes and neuroinflammatory responses between males and females, derived from both sexual chromosomes and hormones [12]. Indeed, estrogens have a profound impact on stroke outcome and promote microglia resolving phenotype during post-ischemic inflammatory response [117], while the role of testosterone remains controversial [118,119]. Morphological and biochemical parameters pointed to the presence of a higher number of pro-inflammatory microglia in males [120–122].

5.3. Therapeutic opportunities directed against microglia

It was initially hypothesized that drugs generally used to target inflammatory cells and mediators would be beneficial also for dampening microglia in CNS disorders. Strikingly, conventional anti-inflammatory drugs are not effective in neurological disorders, since glucocorticoids do not improve neurologic outcomes and the efficacy of NSAIDs in neurodegenerative and psychiatric disorders is still controversial [123]. While more studies are still needed to clarify this issue, global suppression of microglia reactivity, as that achieved using conventional immunosuppressive and anti-inflammatory drugs, has been suggested to lead to a dysfunctional immune system that lacks the beneficial outcomes of the pro-resolving and anti-inflammatory phenotypes. Thus, a more proper approach would seem to target specific microglial functions, rather than generally dampening cell reactivity. Therefore, drugs that potentiate microglial homeostatic functions, such as clearance of protein aggregates, or normalize impaired functions are under intense study as better options for therapeutic strategies.

Nevertheless, little is known on sexual differences on microglia-directed therapies. Interestingly, poly (ADP-ribose) polymerase (PARP) inhibitors, such as minocycline, known to reduce post-ischemic neuroinflammation and brain damage, only work in male patients leading to better neurological outcomes, as further confirmed in experimental models [124,125]. While immune therapies are being tested to reduce inflammation and improve neurological outcome, the molecular mechanisms explaining the sexual differences in microglia may provide some clues, as female microglia have higher expression of genes related with cell plasticity, control of inflammation and brain repair, which could contribute to neuroprotection. These genes and pathways may represent novel targets for sex-related therapeutic approaches in neuropathology [103]. Increasing evidence supports microglia-targeting therapies, including inhibitors of negative regulators of phagocytosis such as CD22 (Siglec-2) [126] or activators of triggering receptor expressed on myeloid cells (Trem)− 2, an immune receptor primarily expressed by microglia and dysregulated in Alzheimer's disease [127,128]. Whether the pharmacological profile of these agents is sexually dimorphic is still unknown.

6. The emerging immunomodulating role of vascular endothelium

In the context of chronic inflammation and/or infection, PD-L1 is induced as a suppressive signal on hematopoietic, endothelial and epithelial cells. Endothelial PD-L1 expression is increased by interferon-γ (+TNF-α), which suppresses T cell cytokine synthesis. PD-L1 is overexpressed in tumor-associated lymphatic vessels, suggesting that tumors educate the endothelium to avoid immune surveillance and promote tumorigenesis. Accordingly, upregulation of PD-L1 in tumor endothelium blocks transendothelial T-cell migration [129–131]. Recently, Gao et al. [132] reported that PD-L1 in tumors can translocate to the nucleus and actively regulate transcription of an array of immune and inflammatory genes to further modulate the immune response. Moreover, the fetal endothelium mediates escape from the mother's immune system through as yet unclear mechanisms [133]. Overall, these observations point to an immunosuppressant role of the endothelium.

As noted in Section 3 above, the sexual dimorphism of immune checkpoint expression has been previously investigated with cancer tissues. A recent study in primary human vascular endothelial cells (HUVECs) showed that endothelial cell PD-L1 is modulated by pro-inflammatory cytokines, i.e. IL-1β, IL-6, interferon-γ, and vascular endothelial growth factor (VEGF) in a sex-specific fashion. After stimulation with these agents, PD-L1 levels are upregulated solely in cells

from female donors, while being unchanged in those from male donors. Accordingly, exposure to synovial fluids from patients with inflammatory arthritis upregulates PD-L1 levels in HUVECs from female donors only. Furthermore, the vascular endothelium may be a source of soluble (s)PD-L1, whose release is dependent on matrix metalloproteinases and modulated by anti-VEGF agents such as bevacizumab and sunitinib [134]. Of note, sex differences in efficacy and safety outcomes have been reported with a few anti-VEGF agents in the cancer setting (reviewed in [135]). PD-L1 is important to control T cell activation, tolerance, and immune-mediated tissue damage in the context of inflammatory conditions; sPD-L1, released from membrane PD-L1 or via exosomes, likely behaves as an immunosuppressive mediator mimicking the effects of PD-L1.

The question remains if these sex differences are restricted to the HUVEC subtype or if other endothelial cells show the same profile. Further, PD-L1 is expressed in other cell types, and it is unclear whether these gender differences occur in these different cell types. However, the dimorphic response is clearly evidenced, with both cell-associated and soluble PD-L1 forms, thereby providing a further mechanism of sex-specific endothelium-immune cell cross-talk and regulation of immune responses in the vasculature. These findings may have implications for sex-specific immunity, vascular inflammation and response to anti-angiogenic therapy.

7. Sex-specific responses to other immune system modulating drugs

Histamine is produced by a range of cell types and binds to four receptor subtypes [136]. Several agents considered to be histamine receptor antagonists turned out to be partial inverse agonists in humans [137], suggesting novel perspectives in the pharmacological control of histamine function. Sex differences in the expression pattern of histamine receptor subtypes and in functional responses to inflammatory stimuli have been reported in tissues [138–141]. However, whether sex differences occur in the clinical response to histamine receptor-targeting agents is at present unclear.

Glucocorticoids are among the most widely prescribed anti-inflammatory medications worldwide. However, response variation and adverse drug reactions hamper their prolonged use [142], and personalized treatment is not yet established in clinical practice. Preclinical evidence clearly shows sexually dimorphic responses to synthetic glucocorticoids in the rat liver [143], with a large set of genes being modulated solely in males and in females along with other genes modulated in both sexes. Livers from male and female mice also display sexually dimorphic inflammatory gene expression, and hepatic glucocorticoid receptor signaling promotes sex-specific inflammatory responses to lipopolysaccharide [144]. It is conceivable that this may be the case in humans as well. Further sex-oriented research should provide guidance to clinicians in refining precision glucocorticoid therapy.

Immunoablative therapies selectively target one or more immune cell subsets, mainly of T and B cell lineages, and proved to be effective against hematologic malignancies and a variety of autoimmune conditions including MS, vasculitis, myasthenia gravis, type 1 diabetes and some types of autoimmune encephalitis [145]. Likewise, lymphocyte trafficking inhibitors, highly effective in MS and Crohn's disease, act by blocking lymphocyte adhesion/extravasation or by sequestering them in secondary lymphoid tissues, thus preventing CNS infiltration [146]. Other immunomodulatory medications (e.g. glucocorticoids, dimethyl fumarate, glatiramer acetate, type I interferons) work by skewing the immune response toward anti-inflammatory phenotypes, reducing the activity of autoreactive T cells or promoting differentiation of regulatory cells [147–150]. There is a need for adequately powered sex-specific analyses of efficacy and safety of such interventions [151].

Finally, new approaches to type 1 diabetes management include novel biologic therapies such as teplizumab, a humanized anti-CD3e monoclonal antibody [152,153] approved by the FDA in 2022 to delay the onset of stage 3 type 1 diabetes. Teplizumab delays immune-mediated damage of pancreatic β cells and preserves insulin production in the early stages of type 1 diabetes. In a small phase 2 clinical trial, subgroup analysis found that treatment with teplizumab for 2 weeks significantly delays the diagnosis of type 1 diabetes in high-risk females but not males [153]. The overwhelming number of women diagnosed with autoimmune disease over men [154], the well-established autoimmune component of type 1 diabetes [155] and the greater clinical impact of cardiometabolic risk factors in women vs men with type 1 diabetes [156] warrant extensive screening and identification of patients who would benefit from this new treatment strategy.

8. Conclusions

Undoubtedly, immunopharmacology has a broad relevance to modern pharmacology. Autoimmunity and cancer are just a couple of areas of immunology where pharmacological targets can be highlighted. Sex and gender differences impact several aspects of immune-mediated diseases management and should be considered carefully in the course of therapy options. Whilst we have learned much in recent years as to the role sexual dimorphism in immune-related pathophysiology, there remain large gaps in our understanding sex-specific immunopharmacological protocols into clinical guidelines. Regrettably, this aspect is considered only in a small number of studies, and no guidelines currently include sex and gender as determinants of specific recommendations for disease management. Therefore, attention to sex and gender differences in preclinical and clinical studies is not only necessary to achieve equality and inclusivity, but also represents a first concrete step towards personalized medicine. Wider inclusion of women in trials along with pre-clinical and clinical research addressing the biological and sociocultural causes of sex disparities in the efficacy, safety and outcomes of immune system modulating drugs are needed to tailor more accurately pharmacotherapy to women and men.

Author Agreement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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