Review Article
A critical review and bibliometric analysis of immunosuppressive therapy for neuroimmunological disorders, post-1965

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Abstract: The aim of this bibliometric analysis was to identify the characteristics and hotspots of scientific research on immunosuppressive therapy for neuroimmunological disorders. Publications were retrieved from the Science Citation Index-Expanded (SCI-E) of the Web of Science (WOS) from 1965 to 2018. Bibliometric parameters, namely, citation numbers, journals, article types, country proportions, increase pattern and research hotspots, were extracted and analyzed by Excel and VOSviewer software. In total, 10,181 papers were included, which were cited 285,022 times, with an average of approximately 28.00 citations per paper. English was the predominant language used, and the US published the largest number of articles (n = 2659). A total of 10,220 author keywords appeared 34,333 times in the retrieval, and “multiple sclerosis” was the most frequent term (n = 2626). In addition, novel immunosuppressive therapy was the pivotal research direction. Large, multicenter, randomized, placebo-controlled trials were needed to assess the efficacy of these agents in different neuroimmunological disorders.

Keywords: Bibliometric, immunosuppressive therapy, neuroimmunological disorders, hotspots

Introduction

Neurological disorders encompass a broad spectrum of diseases, including disorders of the brain, spinal cord, cranial nerves, peripheral nerves, autonomic nervous system, neuromuscular junction, and muscles [1]. Among these disorders, several require immunosuppressive therapy, including neuroimmunological disorders [2]. This term refers to an etiological category of neurological disorders that are characterized by the dysregulation of the immune system, such as multiple sclerosis, myasthenia gravis, immune-mediated polyneuropathy disorders and idiopathic inflammatory myopathies (IIM) [3]. These disorders are not rare and share common characteristics that are progressive and disabling, which result in a significant social burden [4]. Consequently, treatment paradigms have evolved from the amelioration of symptoms only, into both etiological treatment and symptom treatment, aiming at remission and cure [5].

Immunosuppressive therapy is the cornerstone of the management of these neuroimmunological disorders [6]. In general, immunosuppressive agents can be classified into five groups: glucocorticoids, cytostatics, antibodies, drugs acting on immunophilins and others [7]. During the past decade, an enormous amount of scientific literature about neuroimmunology advances has improved our understanding of these immunosuppressive agents [8]. Many novel agents, such as mycophenolate mofetil (MMF) [9], natalizumab [10] and rituximab [11], have shown better efficacy in many neuroimmunological disorders.

Bibliometrics is a quantitative and statistical method used to analyze the citation frequencies, growth trends and research hotspots of a specific subject [12]. Since the first bibliometric article was published in the Journal of the American Medical Association (JAMA) in 1987, the bibliometric method has evolved [13]. To date, many neurological disorders, such as
Review in immunosuppressive therapy for neuroimmunological disorders

Methods

A comprehensive, bibliographic retrieval was performed from the SCI-E database, accessed through the Web of Science (WOS) platform on Mar. 1, 2016. The time span was between 1965 and 2018. To obtain articles on immunosuppressive therapies of neuroimmunological disorders as much as possible, the following search terms were used: (Immunosuppres* OR Azathioprine OR Cyclosporin* OR Cladribine OR Natalizumab OR “Dimethyl Fumarate” OR Fingolimod OR Rituximab OR Infliximab OR Daclizumab OR Alemtuzumab OR Interferon OR Cyclophosphamide OR Mycophenolate OR “Glatiramer Acetate”) AND (neuropath* OR encephalopath* OR “nervous system vasculitis” OR “multiple sclerosis” OR demyelina* OR “nervous system disease” OR dermatomyositis OR polymyositis OR myopathy* OR neuritis OR encephalitis OR leukoencephalopathy OR neuromyelitis OR myelitis OR “myasthenia gravis” OR polyneuropath*) AND treatment. The original data were extracted for further analysis. Two researchers conducted and verified the bibliographic retrieval independently.

Results

The distribution of publication type and language

The literature search yielded a total of 15,011 publications on immunosuppressive therapies of neurological disorders from January 1965 to March 2018. Among them, 10,181 were scientific articles, comprising 67.8% of the total publications. Other popular document types were reviews (2,676, 17.8%), meeting abstracts (1,038, 6.91%) and proceedings papers (504, 3.36%). The remaining types of publications, such as letters and editorial materials, represented less than 1.67%. Only scientific articles were included for further analysis. The majority of the articles retrieved were in English (9,363, 92.0%), followed by German (319, 3.13%), French (198, 1.94%) and Spanish (158, 1.55%), which corresponded to other bibliometric analyses.

Increased pattern of the articles

The first article, named “Treatment of severe myasthenia gravis with immunosuppressive agents”, was published by Mertens et al. in European Neurology in 1969 [19]. From 1969 to 1990, the number of global publications per year remained low, representing only 0.88% of all articles. The annual number of articles has grown rapidly since 1990. The growing trend from 1990 to 2017 fitted the curves as follows: F(x) = 0.4145×2-1633.8×+2E+06, R² = 0.9875 (Figure 1).

Country proportions and journals

The 10,181 articles originated from 52 countries and territories (Figure 2). We extracted the top 10 countries, which contributed 7,163 publications, accounting for 73.50% of all relevant publications. Six of these countries were in Europe, two were in Asia, and two were in America. The US published the highest number of publications (2,659, 27.29%), followed by Germany (1,003, 10.29%), Italy (840, 8.62%), France (530, 5.44%) and Japan (500, 5.13%). In addition, the top 10 most productive journals are summarized in Table 1. Neurology ranked first and contributed the most articles (373), followed by the Journal of Neuroimmunology (372) and Multiple Sclerosis Journal (278).

Characteristics of the top 10 most frequently cited articles

The top ten articles accounted for 13,396 citations, which represented 4.70% of the total (Table 2). A study by Jacobs et al., published in 1996 [20], was the most cited article (1,885 times), while a study by Polman et al., published in 2006 [21], received the most annual citations (140.33 times). Among these ten articles, eight were related to immunosuppressive therapies of multiple sclerosis, investigating the treatment efficacy of interferon, natalizumab and fingolimod.
Figure 1. Model fitting curves of growth trends of the accumulated number of publications on immunosuppressive therapy for neuroimmunological disorders from 1969 to 2017 worldwide. The fitting equation from 1990 to 2017 is: $y = 0.4145x^2 - 1633.8x + 2E+06$, $R^2 = 0.9875$. Y is the number of articles, and X is the year.
Main research hotspots

To identify the main research hotspots in immunosuppressive therapies for neuroimmunological disorders, author keywords were retrieved from these articles. Then, we integrated some author keywords that represent identical disorders or medicine, such as “natalizumab” and “Tysabri”, “fingolimod” and “FTY720”, “dimethyl fumarate” and “BG12”, etc. A total of 10,220 author keywords appeared 34,333 times, including 7,561 author keywords that appeared only once. Articles before 1988 lacked keywords, so the research hotspots were based on keywords from 1988 to 2017. To determine the research trends in this field, we divided the studies into 5 periods, namely, 1988 to 1993, 1994 to 1999, 2000 to 2005, 2006 to 2011 and 2012 to 2017. Among these keywords, multiple sclerosis was the most frequent term (2,626 times), followed by five mainly used drugs, interferon beta (611 times), natalizumab (396 times), fingolimod (335 times), glatiramer acetate (GA) (330 times) and rituximab (278 times). The top 30 most frequently used author keywords and their rankings in different periods were listed in Table 3, of which 11 keywords were immunosuppressive drugs, and 7 keywords were neuroimmunological disorders. The ranking and percentage of the frequency of author keywords in different periods was symbolized as “R (%)” in Table 3. Author keywords that appeared more than half of the time from 2012 to 2017 were natalizumab (66.2%), fingolimod (85.4%), rituximab (53.2%), progressive multifocal leukoencephalopathy (PML) (61.6%), neuromyelitis optica (NMO) (71.6%), relapsing remitting multiple sclerosis (RRMS) (61.5) and disease modifying therapy (65.5%), which may represent the hotspots in this field.

Author keywords appearing more than 70 times were entered into the VOSviewer software to construct their concurrence network. Overall, 47 terms were set out in the figure and mainly stratified into four clusters (Figure 3A). The green cluster included terms mainly representing central nervous system inflammatory demyelinating diseases (CIDD) and relevant treatments, such as multiple sclerosis, NMO and interferon beta. The red cluster included terms mainly related to other autoimmune diseases and neurological disorders, such as myasthenia gravis, dermatomyositis and polymyositis. The blue cluster included terms about mechanisms of autoimmune disease, such as cytokine, inflammation and neuroprotection. Finally, the yellow cluster included terms about side effects of immunosuppressive treatment, such as PML and John Cunningham (JC) virus.

According to the average of each author keyword appearing each year, VOSviewer coded these terms in different colors (Figure 3B). Terms in blue represented earlier appearances than those in yellow and red. Most neurological disorders were in blue and yellow, such as multiple sclerosis, myasthenia gravis and dermato-
### Table 2. The top 10 papers with the most citation frequency for immunosuppressive therapy publication

<table>
<thead>
<tr>
<th>Title</th>
<th>First author</th>
<th>Journal</th>
<th>Year</th>
<th>Citations</th>
<th>Citation frequency per year</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular interferon beta-1 alpha for disease progression in relapsing multiple sclerosis</td>
<td>Jacobs [20]</td>
<td>Annals of Neurology</td>
<td>1996</td>
<td>1885</td>
<td>85.68</td>
<td>They confirmed that intramuscular interferon beta-1 alpha had a significant beneficial impact in relapsing MS patients and provided a foundation for standard treatment of relapsing multiple sclerosis.</td>
</tr>
<tr>
<td>A reversible posterior leukoencephalopathy syndrome</td>
<td>Hinchey [22]</td>
<td>New England Journal of Medicine</td>
<td>1996</td>
<td>1767</td>
<td>80.32</td>
<td>They reported a reversible syndrome named reversible posterior leukoencephalopathy syndrome that may develop in patients who have renal insufficiency or who are immunosuppressed.</td>
</tr>
<tr>
<td>Interferon beta-1b is effective in relapsing-remitting multiple sclerosis</td>
<td>Duquette [23]</td>
<td>Neurology</td>
<td>1993</td>
<td>1571</td>
<td>62.84</td>
<td>Subcutaneous injection interferon beta-1b at a dose of either 1.6 or 8 MIU every other day was confirmed to be efficacious in the reduction of exacerbation rates for relapsing-remitting MS.</td>
</tr>
<tr>
<td>Randomized double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis</td>
<td>Ebers [24]</td>
<td>Lancet</td>
<td>1998</td>
<td>1487</td>
<td>74.35</td>
<td>Subcutaneous interferon beta-1a was an effective treatment for relapsing-remitting MS in terms of relapse rate and defined disability in a dose-related manner.</td>
</tr>
<tr>
<td>Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis</td>
<td>Cohen [25]</td>
<td>New England Journal of Medicine</td>
<td>2010</td>
<td>1083</td>
<td>135.38</td>
<td>They showed superior efficacy of oral fingolimod at a daily dose of either 1.25 or 0.5 mg for relapsing-remitting MS compared with intramuscular interferon beta-1a at a weekly dose of 30 µg.</td>
</tr>
<tr>
<td>Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial</td>
<td>Paty [26]</td>
<td>Neurology</td>
<td>1993</td>
<td>1080</td>
<td>43.2</td>
<td>Through yearly MRI analyses on relapsing-remitting MS patients, interferon beta-1b was confirmed to have a significant impact on the natural history of MS.</td>
</tr>
<tr>
<td>Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis</td>
<td>Jacobs [27]</td>
<td>New England Journal of Medicine</td>
<td>2000</td>
<td>1032</td>
<td>57.33</td>
<td>Initiating treatment with interferon beta-1a at the time of a first demyelinating event is beneficial for patients with brain lesions on MRI that indicate a high risk of clinically definite multiple sclerosis.</td>
</tr>
<tr>
<td>IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis</td>
<td>Komiyama [28]</td>
<td>Journal of Immunology</td>
<td>2006</td>
<td>973</td>
<td>81.08</td>
<td>They demonstrated that IL-17, rather than IFN-gamma, plays a crucial role in the development of EAE.</td>
</tr>
<tr>
<td>Interferon beta-1b in the treatment of multiple sclerosis final outcome of the randomized controlled trial</td>
<td>Duquette [29]</td>
<td>Neurology</td>
<td>1995</td>
<td>834</td>
<td>36.26</td>
<td>Interferon beta-1b had a persistent beneficial effect on the exacerbation rate and MRI burden of disease and was relatively free of long-term side effects.</td>
</tr>
</tbody>
</table>

MS, multiple sclerosis; MIU, million international units; EAE, experimental autoimmune encephalomyelitis.
myositis, with the exception of NMO and RRMS. On the other hand, red items were mainly immunosuppressive drugs, such as fingolimod and natalizumab.

Discussion

Over the last two decades, marked progress has been made in the area of immunosuppressive therapy for neuroimmunological disorders [30]. To our knowledge, this is the first study that presents a comprehensive bibliometric review on immunosuppressive therapies of neuroimmunological disorders. In this study, we have assessed bibliometric parameters, including citation numbers, journals, article types, country proportions and increased pattern. To detect the most researched topics, research hotspots were highlighted in our study.

Author keyword used in bibliometrics can be used to trace the research trend information and identify hotspots [31]. In this study, a total of 10,220 author keywords appeared 34,333 times. In general, these keywords could be divided into two groups: neuroimmunological disorders and immunosuppressive drugs.

Neuroimmunological disorders

Neuroimmunological disorders were previously identified as several countable disorders, including multiple sclerosis, myasthenia gravis, polymyositis, dermatomyositis and Guillain-Barré syndrome (GBS) [32]. Since then, a broad spectrum of neuroimmunological disorders has steadily grown based on numerous developments in molecular genetics, pathogenesis and diagnosis. Among these disorders, multiple sclerosis remains the predominant entity in

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**Table 3. Top 30 author keywords from 1988-2017 for immunosuppressive therapy publications**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>2626</td>
<td>16 (1.0)</td>
<td>161 (6.1)</td>
<td>451 (17.2)</td>
<td>761 (29.0)</td>
<td>1216 (46.3)</td>
</tr>
<tr>
<td>Interferon beta</td>
<td>611</td>
<td>NA</td>
<td>NA</td>
<td>46 (2.7)</td>
<td>158 (25.9)</td>
<td>211 (34.5)</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>396</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>8 (2.0)</td>
<td>123 (31.1)</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>335</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2 (0.1)</td>
<td>41 (12.2)</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>330</td>
<td>NA</td>
<td>NA</td>
<td>3 (1.0)</td>
<td>77 (23.3)</td>
<td>120 (36.4)</td>
</tr>
<tr>
<td>Treatment</td>
<td>295</td>
<td>NA</td>
<td>NA</td>
<td>31 (10.5)</td>
<td>45 (15.3)</td>
<td>80 (27.1)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>278</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>15 (4.5)</td>
<td>109 (39.2)</td>
</tr>
<tr>
<td>MRI</td>
<td>276</td>
<td>5 (1.0)</td>
<td>21 (7.6)</td>
<td>50 (18.1)</td>
<td>80 (29.0)</td>
<td>117 (42.4)</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>257</td>
<td>10 (3.9)</td>
<td>28 (10.9)</td>
<td>46 (17.5)</td>
<td>87 (23.9)</td>
<td>84 (32.7)</td>
</tr>
<tr>
<td>Interferon</td>
<td>253</td>
<td>8 (3.2)</td>
<td>20 (7.9)</td>
<td>48 (19.0)</td>
<td>85 (33.6)</td>
<td>92 (36.4)</td>
</tr>
<tr>
<td>Cytokine</td>
<td>246</td>
<td>4 (1.6)</td>
<td>41 (16.7)</td>
<td>62 (25.2)</td>
<td>69 (28.0)</td>
<td>67 (27.2)</td>
</tr>
<tr>
<td>PML</td>
<td>185</td>
<td>NA</td>
<td>6 (3.2)</td>
<td>10 (5.4)</td>
<td>54 (12.9)</td>
<td>114 (9.6)</td>
</tr>
<tr>
<td>EAE</td>
<td>178</td>
<td>7 (3.9)</td>
<td>6 (3.4)</td>
<td>25 (10.4)</td>
<td>49 (15.7)</td>
<td>88 (13.9)</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>176</td>
<td>7 (4.0)</td>
<td>9 (5.1)</td>
<td>12 (6.8)</td>
<td>50 (14.8)</td>
<td>75 (16.2)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>176</td>
<td>7 (4.0)</td>
<td>30 (5.0)</td>
<td>28 (16.5)</td>
<td>57 (13.2)</td>
<td>53 (24.0)</td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>155</td>
<td>NA</td>
<td>NA</td>
<td>3 (1.9)</td>
<td>41 (20.6)</td>
<td>111 (10.6)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>146</td>
<td>11 (7.5)</td>
<td>20 (13.7)</td>
<td>27 (18.5)</td>
<td>41 (21.8)</td>
<td>46 (30.5)</td>
</tr>
<tr>
<td>Interferon beta 1a</td>
<td>145</td>
<td>NA</td>
<td>11 (7.6)</td>
<td>45 (9.1)</td>
<td>43 (17.3)</td>
<td>46 (29.1)</td>
</tr>
<tr>
<td>RRMS</td>
<td>143</td>
<td>NA</td>
<td>4 (2.8)</td>
<td>20 (14.0)</td>
<td>30 (21.0)</td>
<td>88 (12.6)</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>141</td>
<td>4 (2.8)</td>
<td>22 (15.6)</td>
<td>35 (24.8)</td>
<td>40 (28.4)</td>
<td>39 (27.7)</td>
</tr>
<tr>
<td>Interferon gamma</td>
<td>136</td>
<td>5 (3.7)</td>
<td>26 (19.1)</td>
<td>41 (30.1)</td>
<td>27 (43.9)</td>
<td>32 (51.2)</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>131</td>
<td>4 (3.1)</td>
<td>14 (10.7)</td>
<td>32 (14.4)</td>
<td>32 (31.4)</td>
<td>48 (27.6)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>129</td>
<td>1 (0.8)</td>
<td>6 (4.65)</td>
<td>22 (17.1)</td>
<td>34 (26.4)</td>
<td>64 (18.9)</td>
</tr>
<tr>
<td>Disease modifying therapy</td>
<td>128</td>
<td>NA</td>
<td>NA</td>
<td>3 (2.3)</td>
<td>44 (16.4)</td>
<td>84 (15.6)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>123</td>
<td>2 (1.6)</td>
<td>8 (6.5)</td>
<td>24 (19.5)</td>
<td>33 (20.6)</td>
<td>55 (23.4)</td>
</tr>
<tr>
<td>Therapy</td>
<td>118</td>
<td>3 (2.5)</td>
<td>9 (7.6)</td>
<td>32 (13.7)</td>
<td>42 (18.3)</td>
<td>31 (24.6)</td>
</tr>
<tr>
<td>Interferon beta 1b</td>
<td>115</td>
<td>NA</td>
<td>13 (11.3)</td>
<td>30 (26.1)</td>
<td>29 (37.5)</td>
<td>42 (36.5)</td>
</tr>
<tr>
<td>Neutralizing antibodies</td>
<td>110</td>
<td>NA</td>
<td>4 (3.6)</td>
<td>19 (17.3)</td>
<td>50 (14.5)</td>
<td>37 (42.3)</td>
</tr>
<tr>
<td>IVIg</td>
<td>105</td>
<td>3 (2.9)</td>
<td>13 (12.4)</td>
<td>18 (29.1)</td>
<td>41 (31.9)</td>
<td>30 (28.6)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>105</td>
<td>NA</td>
<td>12 (11.4)</td>
<td>19 (18.1)</td>
<td>34 (29.3)</td>
<td>32 (30.5)</td>
</tr>
</tbody>
</table>

NA, not available; TP, total articles; R (%), ranking and percentage of author keywords; PML, progressive multifocal leukoencephalopathy; EAE, experimental autoimmune encephalomyelitis; RRMS, relapsing remitting multiple sclerosis; IVIg, intravenous immunoglobulin.
Review in immunosuppressive therapy for neuroimmunological disorders
Review in immunosuppressive therapy for neuroimmunological disorders

Figure 3. Map of keywords appearing more than 70 times on immunosuppressive therapy for neuroimmunological disorders. A. The size of the circle represents the frequency of the keyword, and the colors represent groups of terms that are strongly linked to each other. These keywords were divided into four clusters: cluster 1, “CIDD and relevant treatments”; cluster 2, “other neuroimmunological disorders except CIDD”; cluster 3, “mechanism of autoimmune disease”; and cluster 4, “side effects of immunosuppressant treatment”. B. Colors represent the earlier (blue color) or later (red color) years based on the average time of the appearance of each keyword.

terms of social burden and prevalence [33]. In our study, multiple sclerosis, the most frequently observed author keyword, appeared 2,626 times. Moreover, RRMS, one of the main subtypes of multiple sclerosis according to clinical courses, appeared 143 times. Another type of CIDD, NMO, once regarded as a rare form of multiple sclerosis before aquaporin-4 (AQP4) antibodies were found, appeared 155 times. To discriminate NMO from multiple sclerosis beginning with optic neuritis and myelitis, diagnostic criteria of NMO was first published in 1999 [34] and then revised in 2006 [35] and 2015 [36]. These advances have made NMO one of the research highlights of CIDD, and a series of new concepts have been raised, such as NMO spectrum disorder (NMOSD) [37] and clinically isolated syndrome (CIS) [36]. The clinical courses of these two conditions are similar and include relapse and remission. For acute events, high-dose, intravenous methylprednisolone, intravenous immunoglobulin (IVIg) and plasma exchange may improve relapse symptoms and restore neurological functions [38]. For long-term therapy, immunosuppressive treatment is indispensable in preventing further attacks. According to a network meta-analysis published in 2015, moderate- to high-quality evidence (Grading of Recommendations Assessment, Development and Evaluation, GRADE) suggests that alemtuzumab, natalizumab, fingolimod and dimethyl fumarate can reduce relapsing in RRMS, and natalizumab is even associated with a lower risk of condition worsening [39]. These immunosuppressive drugs have changed the treatment protocols of RRMS over the last 20 years. However, many people living with RRMS cannot access these medications because of their high costs [40]. On the grounds of a cost-utility analysis published in 2018, natalizumab and ocrelizumab dominated the other immunosuppressive drugs with more quality-adjusted life-years for lower costs, which may make them a preferred choice for RRMS patients [41].

On the other hand, evidence on the long-term immunosuppressive treatment of NMO is relatively sparse and retrospective. Even so, azathioprine (AZA) and rituximab are still recommended as first-line therapies for NMO [42]. In 2017, an observational study compared the efficacy and tolerability of MMF and AZA and reported no significant differences in maintaining a relapse-free state, but fewer and milder adverse events were attributed to MMF than AZA [43]. This study indicates that MMF may be a better choice than AZA for NMO patients. Other novel agents, namely, tocilizumab and eculizumab, have reported promising results showing an improvement of annualized relapse rates and moderate adverse effects for NMO [44]; however, these treatment recommendations are mainly based on retrospective case-series, and prospective controlled trials are needed to assess their effectiveness in treating this incurable disease.

Other than CIDD, myasthenia gravis, another conventional type of autoimmune disease that is characterized by fluctuating muscle weakness and fatigue, appeared 257 times. Due to the detection of autoimmune antibodies against the acetylcholine receptor (AChR) [45], muscle-specific kinase (MuSK) [46] and lipoprotein-related protein 4 (LRP4) [47], myasthenia gravis is now identified as a B-cell-mediated disease. Immunosuppressive treatment is necessary for patients who do not adequately respond to pyridostigmine [48]. Corticosteroids and cyclosporine were the preferred immunosuppressant, and MMF and AZA were used as second-choice agents [49]. In addition, small case series indicate satisfactory efficacy of rituximab, particularly in AChR antibody-negative, MuSK antibody-positive patients [50]. Another two relatively uncommon neuroimmunological disorders are dermatomyositis and polymyositis, which appeared 176 times and 131 times, respectively. These two diseases are subtypes of IIM and can result in persisting muscle weakness with significant disability [51]. Corticosteroids are the principal treatment to IIM, while other immunosuppressive agents, such as infliximab and AZA, have not
shown certain efficacy due to a lack of high-quality RCTs [52].

Nevertheless, not all neuroimmunological disorders require immunosuppressant treatment. GBS is known as a neuroimmunological disorder with an autoantibody response against the outer surface of the Schwann cell since four ganglioside antibodies were found, namely, GM1, GD1a, GT1a, and GQ1b [53]. Both B and T lymphocytes are likely to play a role in the different stages of GBS. In this respect, immunosuppressant treatment in GBS seems reasonable. In contrast, either oral corticosteroids or intravenous methylprednisolone has been shown to be invalid in the treatment of patients with GBS [54]. In addition to glucocorticoids, MMF, a relatively new immunosuppressive agent and suppressor of B and T lymphocytes, displayed no additional value either [55]. Compared to immunosuppressant treatment, plasma exchange [56] and IVIg [57] have shown significant benefit and availability, and IVIg is the preferred treatment. The reason for the ineffectiveness of immunosuppressant treatment may be due to the acute, one-way course of GBS and pattern of ganglioside antibodies, which are mainly of the Immunoglobulin G (IgG) subclass.

Other rare neuroimmunological disorders, such as multifocal motor neuropathy (MMN) and IgM anti-myelin-associated peripheral neuropathy, have responded to some novel agents, such as rituximab, cladribine and fludarabine, in several uncontrolled studies [58]. Nevertheless, these flawed and variable conclusions are insufficient to support the use of immunosuppressant therapies in clinical settings. Thus, large and well-designed, randomized trials are needed to assess the efficacy of novel immunosuppressant treatment for disorders with uncertain efficacy.

**Immunosuppressive drugs**

According to the different mechanisms and structures, immunosuppressive drugs can be divided into five groups, namely, glucocorticoids, cytostatics, antibodies, drugs acting on immunophilins and others [59]. Other than glucocorticoids, commonly used immunosuppressive drugs in clinical settings are interferons, GA, natalizumab, rituximab, cyclophosphamide (CTX), MMF and AZA. Interferons, another frequently used author keyword that appeared 1,260 times, represent a family of cytokines that were originally named for their ability to “interfere” with viral replication and can be classed into three subfamilies, namely, type I, type II, and type III [60]. Interferon beta was initially used as a first-line therapeutic for the treatment of RRMS 20 years ago. To date, subcutaneous interferon beta is still the most commonly used drug for RRMS, reducing relapse rates by approximately 35% and extending remission periods [61]. The mechanism of how interferon beta works is still unclear. Potential mechanisms include the inhibition of immune cell trafficking across the blood-brain barrier, the regulation of immune cell activation and proliferation, triggering T-cell apoptosis and possibly also neuroprotective effects [62]; however, the usage of interferon beta in neuroimmunological disorders is restricted to multiple sclerosis. Previously, interferon beta was tried as a therapeutic for NMO, but it turned out to be ineffective and even harmful in some cases [63]. Another widely used first-line therapeutic for RRMS is GA. The mechanism of action for GA probably includes the inhibition of the immune response to myelin basic protein and other myelin antigens [64]. A meta-analysis published in 2016 compared the effects of interferon beta and GA in the treatment of people with RRMS and found no significant difference in disease relapse and progression [65]. The efficacy of GA in other neuroimmunological disorders is unclear and not recommended.

Unlike those conventional drugs, monoclonal antibodies are a new generation of drugs for immunosuppressive therapy, represented by natalizumab and rituximab. Natalizumab is a kind of humanized monoclonal antibody against alpha-4 integrin on the surface of lymphocytes, inhibiting the entry of CD4+ and CD8+ T lymphocytes into the brain through the blood-brain barrier [66]. Natalizumab is the first and, to date, the only monoclonal antibody that is approved by the US Food and Drug Administration (FDA) for the treatment of RRMS, which could reduce the annual relapse rate by approximately 60% [67]; however, natalizumab fails to control disease activity in patients with NMO and other neuroimmunological disorders [68]. Rituximab is a type of anti-CD20 B-cell depleting agent, similar to ocreli-
zumab and ofatumumab [69]. In a retrospective study published in 2018, rituximab was compared to all other treatments in a cohort of RRMS, showing better efficacy and drug discontinuation than other commonly used immunosuppressive drugs in patients with newly diagnosed RRMS [70]. Rituximab is also used as first-line therapy for NMO. In a retrospective analysis, NMO patients receiving rituximab presented a 97% decrease of annualized relapse rate and was well tolerated [71]. This result is inspiring but also dubious because of the small scale of the study. Other than CIDP, rituximab also shows good efficacy in other neuroimmunological disorders, such as myasthenia gravis [50] and IIM [72].

Considering the side effects, however, immunosuppressant treatment is a double-edged sword. Therefore, physicians have historically been reluctant in regard to the usage of immunosuppressive drugs. In addition to the many side effects, which include conditions such as hypertension, hyperglycemia, peptic ulcers, and liver and kidney injury, immunodeficiency, resulting in increased susceptibility to infections and higher risk of cancer, is a major concern [73]. Natalizumab was initially approved by the FDA in 2004 but was withdrawn in 2005 because three participants in the drug’s clinical trials developed PML [74]. PML is an opportunistic demyelinating brain disease caused by JC virus infection after immune deficiency. Although natalizumab was subsequently approved again by FDA in 2006, positive JC virus serology results remain the primary cause for therapy discontinuation. Prior to 2015, there were 563 confirmed cases of PML during natalizumab therapy for multiple sclerosis [75]. The overall incidence was almost four per 1,000 patients treated.

For classical, cytotoxic, immunosuppressive drugs such as CTX and AZA, the major side effect is the increase in risk of cancer due to impaired immune surveillance, facilitation of oncogenic viruses and alterations to DNA [76]. Many publications have reported that chronic immunosuppression with AZA increases the risk of malignancy in humans, especially for long-term (>10 years) treatment, and high cumulative CTX doses are associated with an increased risk of bladder cancer and lymphomas [77]. In a prospective study on a cohort of CTX treated multiple sclerosis patients, the cumulative incidence of cancer after CTX treatment was 3.1% at 5 years and 5.9% at 8 years, which revealed no statistically significant difference compared with the general population [78]. This negative result, apparently contradictory to traditional concepts, may be explained by the low cumulative doses that patients received. As for the newest immunosuppressive drugs, such as dimethyl fumarate, rituximab and ocrelizumab, no risk of cancer has been reported. Nevertheless, a strict, long-term follow-up must be planned in patients taking immunosuppressive drugs to avoid a potential risk of cancer.

Limitations

There are several limitations to this study. First, we only recruited papers in English and may have missed some important research published in other languages. Secondly, we may have missed a considerable amount of papers published in non-SCI journals, since the data in this study were only collected from SCI-E in WOS. Third, the search strategy was not perfect for either “neuroimmunological disorders” or “immunosuppressive drugs” due to difficulty to summarize. To compensate for this pitfall, another study representing the whole global research output in this field is needed to make a thorough review on immunosuppressive therapies of neuroimmunological disorders.

Conclusions

Over the last two decades, marked progress has been made in the area of immunosuppressive therapy in neuroimmunological disorders. Treatment options have grown from the use of steroids only to the use of recombinant cytokines, monoclonal antibodies and other compounds specifically targeting committed steps of an evolving autoimmune reaction. However, most neuroimmunological disorders are still incurable. Novel immunosuppressive therapy is one of the pivotal research directions, but for many indications, the efficacy is only documented by small studies. Thus, large, multi-center, randomized, placebo-controlled trials should be performed to assess the efficacy of these agents in different neuroimmunological disorders.

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