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Published in:
Journal of the American Academy of Dermatology

DOI:
10.1016/j.jaad.2021.11.061

Publication date:
2022

Insights into clinical and diagnostic findings as well as treatment responses in patients with mucous membrane pemphigoid: A retrospective cohort study

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Background: The variable clinical severity of mucous membrane pemphigoid (MMP) often leads to diagnostic and therapeutic delays.

Objective: To describe the characteristics of a large cohort of patients with MMP.

Methods: A retrospective review of clinical and diagnostic characteristics as well as treatment responses in 145 patients with MMP.

Results: Monosite involvement was seen in 41.4% and multisite involvement in 58.6% of the patients. The oral mucosa was affected in 86.9% of the patients, followed by the ocular mucosa (30.3%), skin (26.2%), genital mucosa (25.5%), nasal mucosa (23.4%), and pharyngeal and/or laryngeal mucosa (17.2%). Ocular disease developed during the disease course in 41.7% of patients with initially other mucosal site involvement. The malignancy rate was significantly higher in patients with autoantibodies against laminin-332 than in patients with MMP without laminin-332 autoantibodies (35.3% vs 10.9%, respectively; $P = .007$). Systemic immunosuppressive or immunomodulatory therapy was administered to 77.1% of the patients, mainly to patients with multisite ($P < .001$), ocular ($P < .001$), and pharyngeal and laryngeal involvement ($P = .002$). The remaining patients (22.9%) received topical therapy. Adverse events were frequently reported.

Limitations: Retrospective design.

Conclusion: Patients with MMP present with a heterogeneous clinical presentation, and new symptoms may develop during the disease course. Cancer screening should be considered for patients with MMP and, in particular, for those with autoantibodies against laminin-332. (J Am Acad Dermatol 2022;87:48-55.)

Key words: autoimmune blistering disease; autoimmune bullous diseases; case series; clinical characteristics; immunology; laminin-332; malignancy; mucous membrane pemphigoid.

INTRODUCTION

Mucous membrane pemphigoid (MMP) comprises a group of heterogeneous, autoimmune blistering diseases, with predominant mucosal involvement, characterized by autoantibodies directed against structural proteins—including bullous pemphigoid (BP) 180, BP230, laminin-332, type VII collagen, and $\alpha 6$ and $\beta 4$ integrin

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Funding sources: None.
IRB approval status: Reviewed and approved by the institutional review board; approval 2018/530.
Accepted for publication November 22, 2021.
Reprints not available from the authors.
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Published online December 9, 2021.
0190-9622

https://doi.org/10.1016/j.jaad.2021.11.061

subunits—in the epidermal basement membrane zone.[1-3] Involvement of ≥1 mucosal sites may occur, making MMP a clinically heterogeneous disease. Various terms were previously used to define MMP, including benign mucous membrane pemphigoid and (ocular) cicatricial pemphigoid. According to The First International Consensus on MMP and the recently published European guideline on MMP, MMP is the appropriate terminology for this disease and older terminologies should be avoided.[1,4] The clinical severity of MMP is highly variable, ranging from mild oral inflammation or conjunctivitis to severe complications, such as progressive conjunctival cicatrization, which may culminate in blindness or a life-threatening laryngeal obstruction without treatment.

CAPSULE SUMMARY

- Mucous membrane pemphigoid (MMP) is a group of rare, autoimmune, bullous diseases with highly variable clinical heterogeneity and potential diagnostic delays.
- Lesions in other mucosal sites may develop in patients with MMP during follow up. Clinicians should be aware of the potential occurrence of malignancies in patients with MMP with autoantibodies against laminin-332.

The diagnosis of MMP is based on a mucosal and/or skin biopsy using direct immunofluorescence (DIF) microscopy, which helps detect linear deposition of autoantibodies along the epidermal basement membrane zone. In addition, indirect immunofluorescence (IIF) microscopy performed on human salt-split skin (SSS) and several immunoserologic tests can help detect circulating autoantibodies in the serum.[1] Systemic immunosuppressive and immunomodulatory drugs are a part of the management of MMP and can be administered as monotherapy or combined with other drugs depending on the severity of the disease.[1,5,6]

Large, retrospective case studies on MMP are scarce and have been mainly conducted in patients with oral or ocular involvement.[7,8] The aim of this study was to describe clinical and diagnostic findings as well as treatment responses in patients diagnosed with different subtypes of MMP to support early recognition and improve patient care.

MATERIALS AND METHODS

Study design

This single-center, retrospective study included patients diagnosed with MMP between 2002 and 2019 at the Center for Blistering Diseases in Groningen, the Netherlands. Eligible participants were included based on previously described criteria.[9] Laboratory techniques and interpretation of DIF, IIF performed on SSS, immunoblot, and enzyme-linked immunosorbent assay were performed as previously described.[10] The keratinocyte footprint assay (KFA) was retrospectively performed on all patients' sera.[11]

Clinical characteristics were assessed by reviewing the patients' medical records. Data on treatment response and adverse effects of the following therapies were collected: dapsone, cyclophosphamide, azathioprine, mycophenolic acid, and rituximab. Only patients who received these as monotherapy or in combination with short-term prednisone were assessed. Early and late clinical outcomes, ie, disease control (DC) and remission (partial or complete), defined based on an international consensus, were analyzed.[12] Data were collected anonymously from electronic case report forms using OpenClinica software (OpenClinica). Individuals were excluded if they had a diagnosis of cutaneous pemphigoid and if accurate clinical details were missing. The study was approved by the University Medical Center Groningen Medical Ethical Committee. Written consent for the images was provided.

Statistical analysis

All continuous outcomes were described as medians with interquartile ranges (IQRs). Correlations between bivariate outcome measures were analyzed using the χ^2 or Fisher's exact test. Comparisons of the means or medians of unpaired, continuous data were performed using the Mann-Whitney U test. Binary logistic regression was performed to analyze the predictors of malignancy. Statistical significance was defined as a P value of $<.05$. The statistical analyses were performed using SPSS Statistics, version 23 (IBM).

RESULTS

Patient characteristics

Overall, 145 patients diagnosed with MMP were included. The median age at diagnosis was 64.0 years (IQR, 18.0 years), with female predominance (n = 84, 57.9%). In 60 patients (41.4%), the involvement of 1 mucosal site was seen, compared with 85 patients (58.6%) with multisite involvement. The median diagnostic delay was 12.0 month (IQR, 21.8 months). No significant difference was seen in the diagnostic delay between monosite and multisite involvement

Abbreviations used:

BP: bullous pemphigoid
DC: disease control
DIF: direct immunofluorescence microscopy
Ig: immunoglobulin
IIF: indirect immunofluorescence microscopy
IQR: interquartile range
KFA: keratinocyte footprint assay
MMP: mucous membrane pemphigoid
SSS: salt-split skin substrate

([median, 13.5; IQR, 24.5] vs [median, 9.0; IQR, 19.0], respectively; P = .088). The median follow-up time was 26.0 months (IQR, 40.0 months; n = 129).

Clinical findings

Table I presents an overview of the mucosal lesions and symptoms per mucosal site. A majority of the patients with MMP presented with involvement of the oral mucosa (n = 126; 86.9%), followed by the ocular mucosa (n = 44; 30.3%), genital mucosa (n = 37; 25.5%), nasal mucosa (n = 34; 23.4%), and pharyngeal and/or laryngeal mucosa (n = 25; 17.2%) (Fig 1). The diagnosis of pharyngeal and/or laryngeal MMP was made by an otorhinolaryngologist using nasendoscopy and laryngoscopy. Skin involvement was reported in 38 patients with MMP (26.2%), of whom 11 patients with MMP presented with skin lesions preceding mucosal lesions, whereas in 9 patients with MMP, skin lesions developed after mucosal symptoms. Moreover, in 15 of 36 patients (41.7%) with ocular multisite involvement, the ocular symptoms developed after a median of 48.0 months (IQR, 71.0 months) after the first reported symptoms. Patients were referred to the ophthalmology department when ocular symptoms were present to confirm the diagnosis. The clinical characteristics of patients with autoantibodies against laminin-332 (n = 17; 11.7%) consisted of involvement of the oral mucosa (n = 17), nasal cavity (n = 10), conjunctivae (n = 9), pharynx (n = 5), larynx (n = 5), and genital mucosa (n = 2). Multisite involvement was seen more frequently in this subgroup (n = 15, 88.2% vs n = 70, 54.7%, respectively; P = .018), as was male predominance (n = 13, 76.5% vs n = 58, 37.5%, respectively; P = .005; Supplementary Table I, available via Mendeley at https://doi.org/10.17632/dm356kv35j.1.) A malignancy, mainly solid tumors, was reported in 20 of the 145 patients with MMP (13.8%); of them, a malignancy developed during follow up in 9 patients (6.2%) (median, 26.5 months; IQR, 74.3 months). These malignancies included lung carcinoma (n = 3), prostate cancer (n = 1), penile cancer (n = 1), breast cancer (n = 1), endometrial cancer (n = 1), vulvar carcinoma (n = 1), and Non-Hodgkin lymphoma (n = 1). Notably, 6 of 17 patients (35.3%) with autoantibodies against laminin-332 had a malignancy, compared with 14 of 128 patients (10.9%) without these autoantibodies (odds ratio, 6.08; 95% CI, 1.65-22.44; P = .007), adjusted for age, sex, and the use of systemic treatment (Supplementary Table I).

DIF microscopy and histopathology

A biopsy of the perilesional or healthy mucosa and/or skin was performed for all the 145 patients with MMP for DIF, which showed linear deposition of autoantibodies in 137 patients with MMP (94.5%). Linear immunoglobulin (Ig)G deposition was seen in a majority of the patients with MMP (n = 118; 81.4%), in contrast to IgA (n = 82; 57.0%) and C3c (n = 80; 55.2%). Interestingly, the linear deposition of IgA, alone or combined with IgG or C3c, was seen more often in patients with multisite involvement than in those with monosite involvement ([n = 55; 65.5%] vs [n = 27; 45.8%], respectively; P = .002) and in patients with ocular involvement than in those without ocular involvement ([n = 32; 72.7%] vs [n = 58; 54.7%], respectively; P = .013). Linear IgA deposition was also seen more often in patients with MMP who received systemic treatment than in those who received local treatment ([n = 66; 61.7%] vs [n = 12; 38.7%], respectively; P = .043). Histopathology showed a subepithelial split in 56 biopsies (48.7%). Furthermore, eosinophils were observed in 40 biopsies (34.8%) and ulceration or erosions in 33 biopsies (29.0%).

IIF microscopy and serology

IIF was performed on SSS for all the 145 patients with MMP, which showed a positive result in 65 patients (44.8%), of whom 35 patients (53.8%) showed epidermal binding of IgG, 8 (12.3%) showed epidermal binding of IgA, and 9 (13.8%) showed epidermal binding of a combination of IgG and IgA.Dermal binding of IgG and/or IgA was observed in 13 patients (9.0%). KFA was performed in all the 145 patients with MMP, of whom 17 (11.7%) showed autoantibodies against laminin-332. The result of IIF performed on SSS was positive in 12 of 17 of these patients: 3 showed epidermal and 9 showed dermal binding. Supplementary Table II (available via Mendeley at https://doi.org/10.17632/dm356kv35j.1) summarizes the results of the immunoblot and enzyme-linked immunosorbent assay.

Table I. Clinical findings and symptoms of patients with mucous membrane pemphigoid

Oral mucosa (n = 126)	N (%)*	Ocular mucosa (n = 44)	N (%)*	Nasal mucosa (n = 34)	N (%)*	Pharyngeal and/or laryngeal mucosa (n = 25)	N (%)*	Genital mucosa (n = 37)	N (%)*
Monosite involvement	44 (34.9)	Monosite involvement	8 (18.2)	Monosite involvement	0 (0)	Monosite involvement	0 (0)	Monosite involvement	8 (21.6)
Multisite involvement	82 (65.1)	Multisite involvement	36 (81.2)	Multisite involvement	34 (100)	Multisite involvement	25 (100)	Multisite involvement	29 (78.4)
Location of lesions		Location of lesions				Location of lesions			
Gingiva	95 (77.2)	Both eyes	36 (81.8)			Pharynx	19 (76.0)		
Buccal	72 (58.5)	Single eye	8 (18.2)			Larynx	16 (64.0)		
Palatum	55 (44.7)								
Lips	22 (17.9)								
Tongue	21 (17.1)								
Floor mouth	1 (0.8)								
Clinical findings		Clinical findings		Clinical findings		Clinical findings		Clinical findings	
Erosions	93 (75.6)	Symblepharon	37 (84.1)	Hemorrhagic crustae	29 (85.3)	Fibrosis	11 (55.0)	Erosions	24 (64.9)
Blisters	60 (48.8)	Fornix shortening	16 (36.4)	Bleeding	21 (61.8)	Hyperemia	9 (45.0)	Erythema	21 (56.8)
Erythema	54 (43.9)	Trichiasis	16 (36.4)	Erosion	16 (47.1)	Blisters	5 (25.0)	Architecture loss	13 (35.1)
Gingivitis	34 (27.6)	Fibrosis	12 (27.3)			Erosions and/or ulceration	4 (20.0)	Ulceration	4 (10.8)
White lines	22 (17.9)	Ankyloblepharon	7 (15.9)			Crusts	1 (5.0)	Blisters	3 (8.1)
Ulceration	16 (13.0)	Entropion	6 (13.6)						
Fibrosis	3 (2.4)								
Symptoms		Symptoms				Symptoms		Symptoms	
Pain	56 (59.6)	Burning	15 (39.5)			Pain or difficulty swallowing	13 (68.4)	Pain	13 (61.9)
Difficulty eating	36 (38.3)	Redness	12 (31.6)			Difficulty eating	9 (47.4)	Pruritus	9 (42.9)
Pain swallowing	28 (29.8)	Reduced vision	11 (28.9)			Hoarseness	8 (42.1)	Dysuria	6 (28.6)
Bleeding	27 (28.7)	Blindness	2 (5.3)			Painful throat	8 (42.1)	Burning	6 (28.6)
Redness	17 (18.1)	Sand feeling	10 (26.3)			Dyspnea	4 (21.1)	Bleeding	2 (9.5)
Peeling	12 (12.8)	Tears	10 (26.3)					Dyspareunia	2 (9.5)
Discomfort	8 (8.5)	Dryness	6 (15.8)						
Burning	5 (5.3)	Pain	6 (15.8)						
		Photophobia	6 (15.8)						
		Itch	4 (10.5)						

*Percentages were calculated after the exclusion of patients for whom data were unknown.

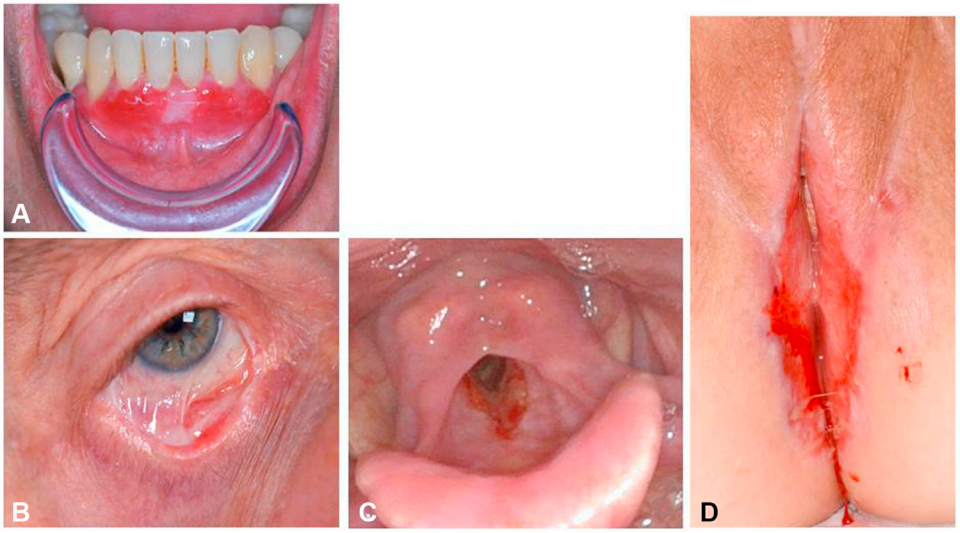

Fig 1. Clinical characteristics of patients with mucous membrane pemphigoid. **A**, Gingivitis. **B**, Symblepharon. **C**, Laryngeal cicatrization and erosions. **D**, Vulvar erosions, fusion of the labia, and architecture loss.

Treatment response

During follow up, a majority of the patients (n = 108; 77.1%) received systemic immunosuppressive or immunomodulatory therapy, with a median number of 2 (IQR, 3.5) systemic therapies, whereas the remaining patients (n = 37; 22.9%) received topical therapy, mainly high-potency corticosteroids. Notably, patients with multisite involvement received systemic therapy more often than those with monosite involvement ([n = 73; 89.0%] vs [n = 35; 60.3%], respectively; $P < .001$). In addition, patients with ocular involvement and patients with pharyngeal involvement alone or combined with laryngeal involvement received systemic therapy more often than those without these involvements ([n = 40, 97.6% vs n = 68, 68.7%; $P < .001$] and [n = 24, 100% vs n = 84, 72.4%; $P = .002$], respectively). Supplementary Table III (available via Mendeley at https://doi.org/10.17632/dm356kv35j.1) summarizes the characteristics of patients with MMP and their responses to immunosuppressive and immunomodulatory treatments. A majority of the patients had multisite involvement. A total of 72 patients received dapsone, of whom 31 achieved DC (43.1%) and 25 achieved remission (34.7%). Cyclophosphamide was administered to 44 patients, of whom 21 achieved DC (47.7%) and 15 (34.1%) achieved remission. Only 6 (22.2%) and 5 (18.5%) patients achieved DC and remission, respectively, with azathioprine (n = 27), and 4 (33.3%) and 2 (16.7%) patients achieved DC and remission, respectively, with mycophenolic acid (n = 12). Finally, 28 patients received rituximab, of whom 18 (64.3%) achieved DC and 15 (53.6%) achieved remission. The reason for cessation of therapy was mainly side effects or ineffectiveness. Almost all patients reported adverse events during the therapy (Supplementary Table IV, available via Mendeley at https://doi.org/10.17632/dm356kv35j.1.)

DISCUSSION

MMP is a group of chronic diseases, with substantial diagnostic delays, mainly due to the highly variable clinical phenotype. This large cohort study of well-defined patients with MMP sought to improve our understanding of the clinical characteristics of MMP. MMP may affect different sites during the disease course. Our results showed that ocular symptoms developed in nearly 42% of patients with ocular multisite involvement later in the disease course. Previously, Higgins et al[13] reported the development of ocular disease in 37% of patients with oral MMP. Therefore, follow-up care, including regular physical examinations and consultations with an ophthalmologist at the first visit and during follow up in case of clinical symptoms, is essential in order to prevent suboptimal treatment and complications.[14] The factors contributing to scar formation in patients with MMP are poorly understood. Inflammatory responses near the lamina densa and papillary dermis may contribute to scar formation.[15] In this study, scarring was mainly seen in patients with ocular, pharyngeal, and laryngeal involvement and was less common in patients with oral involvement; however, during the healing phase, fibrosis might be observable in the oral mucosa.[16-20]

Several reports have shown that a mucosal or skin biopsy for DIF yields the highest sensitivity for the diagnosis of MMP, in contrast to IIF performed on SSS.[7,15,21-24] Histopathology showed a subepithelial split in less than half of the patients and is, therefore, not a useful tool for the diagnosis of MMP. In this study, a positive biopsy result was seen in 94.5% of patients using DIF, and a positive result for IIF performed on SSS was seen in 44.8% of the patients. Interestingly, the deposition of linear IgA alone or combined with IgG or C3c, assessed using DIF, were more frequently seen in patients with multisite involvement than in those with monosite involvement. In addition, patients with ocular involvement showed the linear deposition of IgA more frequently than those without ocular involvement. We also observed that patients with MMP with IgA deposition required systemic therapy more often. A previous study showed that combined IgA and IgG reactivity was associated with a more severe disease course compared with the presence of IgG alone.[25] It has been postulated that IgA, possibly together with IgG, activates a complement-mediated inflammatory response, resulting in the progression of mucosal lesions in patients with MMP.[26]

The pathogenic role of autoantibodies in MMP has been shown both in vitro and in vivo. In more than half of the patients, we found a positive immunoblot result, and a majority of them had IgG or IgA against BP180. Previous studies have confirmed that BP180 is the most frequent target antigen in MMP, detected in majority of MMP sera.[27-29] Laminin-332 is targeted in a subset of patients with MMP, often with multisite involvement—including pharyngolaryngeal and oropharyngolaryngeal involvement.[30,31] Our results showed that 17 of the 145 patients had autoantibodies against laminin-332, as determined using KFA, a specific test to assess the presence of these autoantibodies.[11] Of them, only 9 patients showed dermal binding, determined using IIF performed on SSS, and 5 had a negative result for IIF performed on SSS. Notably, the remaining 3 patients showed only epidermal binding, indicating the combined presence of autoantibodies such as laminin-332 and BP180. Using KFA, we were able to detect more patients with autoantibodies against laminin-332 than those detected using IIF performed on SSS, suggesting that it is a sensitive technique. The potential occurrence of a malignancy in patients with MMP and, in particular, in patients with autoantibodies against laminin-332, is a matter of controversy. Previous studies have shown conflicting results regarding the association of malignant neoplasms in patients with MMP with autoantibodies against laminin-332.[32-35] The rarity of this disease and possible confounders, such as age, the use of immunosuppressive therapy, and the detection technique used for laminin-332 autoantibodies, might have influenced these results. In our series, the malignancy rate was significantly higher in patients with autoantibodies against laminin-332 (35.3%) than in patients with MMP without antibodies against laminin-332 (10.9%). Future prospective, multicenter studies are needed to assess the risk and etiology of malignancies in patients with MMP. However, clinicians should be aware of the potential occurrence of malignancies in patients with MMP and, in particular, those with autoantibodies against laminin-332. Therefore, oncologic screening is recommended, in particular for solid tumors, at the time of initial diagnosis and on indication during follow up.[4]

Systemic immunosuppressive and immunomodulatory therapies are often required to cease inflammation and stop the progression of scarring. In this study, patients with multisite involvement and patients with ocular involvement required systemic therapy more often, indicating a more severe disease course. Moreover, the involvement of the pharynx or larynx was also associated with the administration of systemic therapy because these locations are difficult to reach with topical treatment. Previous studies have reported satisfactory results with dapsone, cyclophosphamide, azathioprine, and mycophenolic acid in patients with MMP depending on the severity.[36-40] We found rather poor results, with the remission percentages between 16% and 35% with and without short-term prednisone. However, a direct comparison of endpoints is difficult because several studies used different outcome measures. Patients and clinicians should be aware of the side effect profile of these immunosuppressive drugs. Rituximab, a monoclonal anti-cluster of differentiation 20 antibody, is increasingly being used in patients with refractory MMP. Our data showed a remission rate of 54% in patients treated with different dosages of rituximab. Previously, Lamberts et al[41] evaluated the effectiveness of rituximab in the treatment of MMP in more detail at our center, showing partial remission in 65% and complete remission in 29% of patients but with a high relapse rate (75%). Other biologics, such as intravenous Ig and tumor necrosis factor-α inhibitors, are used in recalcitrant cases and are considered as third- and fourth-line therapies, respectively.[14] Further prospective studies are needed to position and compare these drugs in the treatment of MMP.

The strengths of this study include the considerably large sample size and the comprehensive clinical data. The limitations of this study are its

retrospective design; the lack of disease severity measurements, such as the MMP disease area index; and the lack of patient-reported outcome measures during follow up. Long-term follow up is critical for providing longitudinal data on treatment outcomes and alterations in the clinical course of this chronic disease. However, our study provided relevant data on the early and late endpoints of the systemic therapy administered during a median time of 26 months.

In summary, symptoms in other mucosal sites in patients with MMP, such as ocular disease, might develop during the disease course. Therefore, patients with MMP should be regularly monitored by a multidisciplinary team. Because of the possible increased risk of malignancy in patients with MMP and, in particular, those with autoantibodies against laminin-332, cancer screening should be considered for these patients. Systemic immunosuppressive or immunomodulatory therapy was mainly administered to patients with multisite, ocular, as well as pharyngeal and laryngeal involvement. The rather moderate treatment response and frequent adverse events emphasize the need for early recognition, diagnosis, and prevention of the progressive disease course of MMP.

Conflicts of interest

Dr Horváth reports fees from Janssen-Cilag (advisory boards, educational grants, consultations, investigator initiative studies), AbbVie (advisory boards, educational grants, consultations, investigator initiative studies), Novartis Pharma (advisory boards, consultations, investigator initiative studies), UCB Pharma (advisory boards, consultations), Leo Pharma (consultations), Solenne B.V. (investigator initiative studies), Celgene (consultations, investigator initiative studies), Akari Therapeutics (consultations, investigator initiative studies), Philips (consultation), Roche (consultation), Regeneron (consultation), and Sanofi (consultation). Drs Rashid, Meijer, Bolling, Diercks, and Pas have no conflicts of interest to declare.

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