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Methylprednisolone aceponate* in eczema and other inflammatory skin disorders – a clinical update

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SUMMARY

Methylprednisolone aceponate (MPA) has been shown to provide rapid, reliable and highly effective treatment of eczematous disorders, with an efficacy comparable to that of most reference topical corticosteroids. It also has excellent local and systemic tolerability. MPA is effective in the treatment of facial and scalp eczema and sunburn and has shown promising results in the treatment of psoriasis. Its rapid efficacy and lack of undesirable local and/or systemic side effects make MPA particularly suitable for use in children and infants. The wide range of formulations (0.1%) of MPA, including cream, ointment, fatty ointment, milk and solution, enable treatment to be tailored to the individual patient. In addition, MPA has the advantage of once-daily application compared with twice-daily treatment for other topical corticosteroids, thereby improving patient safety and promoting patient compliance but without compromising efficacy.

Keywords: Eczema; lipophilicity; methylprednisolone aceponate; paediatric; topical corticosteroid

INTRODUCTION

The observation in the early 1950s that hydrocortisone was useful in the topical therapy of inflammatory and proliferating skin disorders has revolutionised the treatment of eczema – a condition that affects approximately 20% of the population and is the most common indication in dermatology (1–4). Following the introduction of initial low-potency agents, higher potency corticosteroids were developed. However, higher potency was associated with an increased risk of systemic and topical side effects. Then, in the 1990s, the association between increased potency and increased side effects was uncoupled, with the development of the fourth generation topical corticosteroids (5).

Methylprednisolone aceponate (MPA) (Advantan®; Intendis GmbH, Berlin, Germany) is a fourth generation topical corticosteroid, which has been developed to provide potent but gentle treatment with high local efficacy and excellent tolerability in terms of systemic and local side effects, including a low potential for skin atrophy (5). In clinical studies involving more than 1900 patients, signs of atrophy were observed in only two cases, both of which probably involved 'therapeutic demasking' of pre-existing atrophy, once inflammation had subsided following treatment with MPA (5).

MPA is indicated for a wide range of eczematous conditions, including atopic dermatitis, contact eczema, seborrhoeic eczema, degenerative eczema and eczema in children and infants. It is also suitable for the treatment of sunburn and has been used to effectively treat psoriasis.

The wide range of MPA formulations, including a cream, ointment, fatty ointment, milk emulsion and an alcoholic solution, make it suitable for a variety of skin types and conditions, including acute, subacute and chronic phases of eczema, as well as large or hairy areas. MPA is also suitable for occlusive treatment, which is sometimes necessary to prevent excoriation and to keep medication in place over an affected area (5,6).

In addition, MPA has the advantage of once-daily application compared with twice-daily treatment for other topical corticosteroids (e.g. betamethasone valerate), thereby improving patient safety and compliance but without compromising efficacy (5,7,8).

MATERIALS AND METHODS

Mechanism of Action

MPA (21-acetoxy-11β-hydroxy-6α-methyl-17-propionyloxy-1,4-pregnadiene-3,20-dione) is a non-halogenated, diester corticosteroid, specifically designed to treat eczema. As one of the fourth generation topical corticosteroids, the efficacy of MPA can be compared with that of the classic corticosteroid,

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betamethasone valerate; the tolerability of MPA, however, is much closer to that of hydrocortisone butyrate.

The process of developing MPA has involved modifications to the prednisolone molecule (5), including the introduction of a methyl group at C6, which is associated with a higher intrinsic activity of MPA (Figure 1). Furthermore, the absence of a halogen (fluorine or chlorine) atom at C6 and/or C9 of the steroid moiety, which is often found in potent topical corticosteroids, may be responsible for the high degree of dissociation between the topical therapeutic effects of MPA and systemic side effects (5). In addition, the introduction of two ester groups at C17 and C21 (double esterification) has resulted in a highly lipophilic molecule, which permits efficient and rapid penetration into the stratum corneum (9) and therefore higher concentration at the site of therapeutic activity in the skin (10). Highly lipophilic agents, such as MPA, do not, as a rule, attain high serum concentrations (10), thus reducing the potential for systemic effects.

Once absorbed into the skin, MPA is hydrolysed to its principal metabolite, methylprednisolone 17-propionate (MPP) by esterases of the skin. The parent compound, MPA, has 2.4 times higher affinity for the corticosteroid receptor than hydrocortisone (11), whereas the active metabolite, MPP, has 6.1 times higher affinity for the corticosteroid receptor than hydrocortisone (11). Moreover, the bioactivation of MPA is accelerated in damaged and inflamed skin compared with normal skin because of the relatively higher levels of esterases found in inflamed skin (11,12), thus increasing the concentration of the active MPP even further at the therapeutic site.

Following systemic absorption, MPP is rapidly inactivated by conjugation with glucuronic acid to the inactive MPP glucuronide and is excreted mainly in the urine, thus reducing the potential for inducing systemic side effects (11).

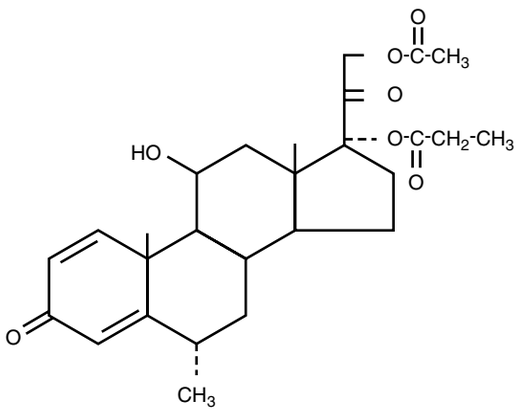

Figure 1 Chemical structure of methylprednisolone aceponate (MPA). The double esterification at C17 and C21 enhances lipophilicity, enabling rapid penetration into the stratum corneum. The methyl group at C6 is associated with a higher intrinsic activity. One gram Advantan® contains 1 mg (0.1%) of MPA

RESULTS

Efficacy

According to Miller and Munro's classification of potency (13), MPA is a potent topical corticosteroid (category 2) and is more effective than betamethasone valerate (14). Using the UVB erythema inhibition test, the study of 165 volunteers with healthy skin compared 0.1% MPA cream, fatty ointment and ointment with the appropriate formulations of other, potent, topical corticosteroids. The potency of MPA has been confirmed in other *in vivo* studies (15).

In comparison with reference topical corticosteroids (betamethasone valerate), once-daily MPA has been shown to be a highly effective treatment for eczema. Six multicentre, controlled, double-blind trials were conducted in 1723 adult patients with eczematous disorders. In each trial, treatment was carried out for a maximum of 3 weeks, with the attending physician deciding whether MPA cream or ointment was appropriate.

In the trials, MPA cream or ointment, administered once daily, was shown to be as effective as twice-daily treatment with betamethasone valerate cream, with successful treatment achieved in 92.6% (138/149) of patients using MPA cream and 92% (138/150) of patients using MPA ointment vs. 95.5% (279/292) using twice-daily betamethasone valerate cream (5,7).

The results also showed that once-daily MPA was as effective as twice-daily MPA (5,7). Once-daily application of MPA achieved similar efficacy to twice-daily application of MPA, with 92% (133/144) of patients treated successfully vs. 90% (121/135), respectively (5,7). MPA cream was shown to perform as equally well as MPA ointment, with successful results in 88% (127/145) of patients treated with MPA cream vs. 86% (118/137) of patients treated with MPA ointment.

Overall, therapeutic success (distinct improvement or healing) was achieved in a total of 91% (1038/1145) of patients with MPA cream or ointment (5). Once-daily MPA cream or ointment was shown to be a potent topical corticosteroid, which was equally effective as twice-daily betamethasone valerate in the treatment of eczematous disorders (Figure 2).

The excellent efficacy of once-daily treatment with MPA was confirmed by a large, observational study of MPA treatment (cream/ointment/fatty ointment) in 2059 patients with eczema aged between 2 months and 87 years. The main indications included atopic dermatitis (38.6%), acute contact dermatitis (26.7%), exsiccation eczema (3.9%) and other non-specific types of eczema (22%) (16). After 5.5 days, a distinct improvement was seen in 74% of patients, with symptoms clearing in almost 5%. After 12.4 days, approximately 40% of patients no longer required treatment (16). The symptoms, reddening and itching, which were rated as mainly severe or moderately severe at the beginning of treatment, showed distinct regression, with the percentage of

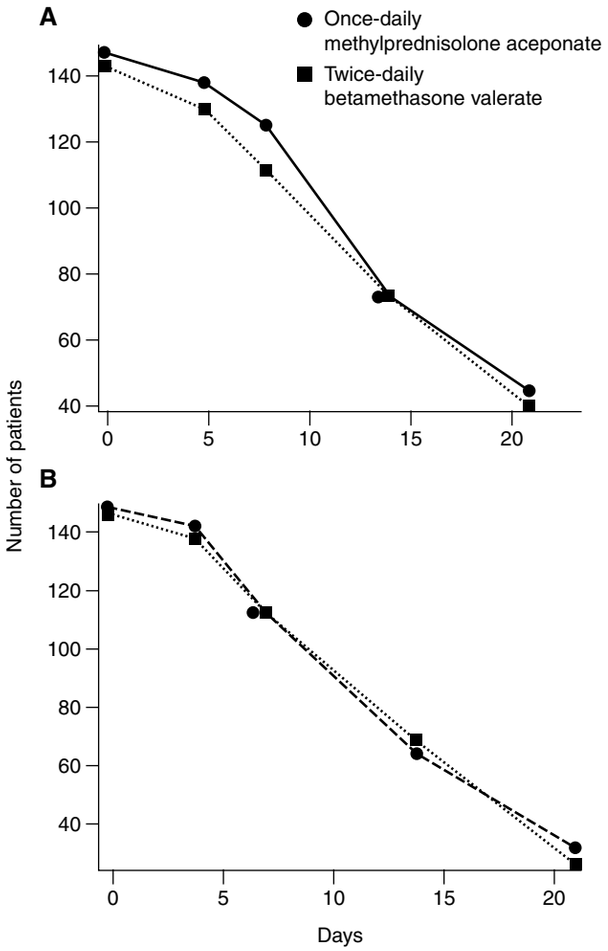

Figure 2 Clearance rates of 'erythema' in patients treated with (A) cream formulations and (B) ointment formulations. [Adapted from Fritsch (7), reprinted with permission]

patients showing severe reddening decreasing from 48 to 1% and those with moderate reddening decreasing from 42 to 7%. In addition, the percentage of patients with severe itching decreased from 57 to 1% and those with moderate itching decreased from 31 to 5.5% after treatment. Other symptoms, such as weeping/crusting, lichenification and burning, showed less pronounced regression because of their lower initial incidence and severity.

The onset of effect was rated as very rapid in almost one-third of patients and as rapid in half of patients. Rapid onset of action of MPA, as indicated by relief of erythema, has also been reported by Fritsch (7). Clearance of erythema during 3 weeks of treatment was shown to be more rapid with once-daily MPA cream or ointment than with twice-daily betamethasone valerate cream (7).

Tolerability

Although MPA is a potent topical corticosteroid (14), it has low atrophogenic potential (17,18). MPA has shown a favourable benefit/risk ratio, with minimal systemic adverse effects even with long-term use (18,19). According to analysis of clinical trials in MPA (5), adverse drug effects were noted in an average of 4.7% (72/1620) of patients treated with MPA cream, ointment and fatty ointment. This compares with 6.2% (36/578) of patients treated with betamethasone valerate cream, 5.9% (11/188) of those treated with betamethasone valerate fatty ointment and 4.5% (9/198) of patients treated with hydrocortisone butyrate. Termination of therapy because of adverse effects occurred in less than 1% of patients treated with MPA, and no allergic reactions were observed (5).

Local Tolerability

The good local tolerability of MPA has been demonstrated by several studies evaluating the risk of skin atrophy and telangiectasia. In a double-blind, randomised, 8-week, non-occluded application test in 20 healthy volunteers, once-daily MPA cream did not lead to any significant reduction in skin thickness compared to the vehicle. In contrast, however, twice-daily treatment with betamethasone valerate significantly decreased skin thickness (17).

MPA has a more favourable safety profile in healthy volunteers than clobetasol propionate and prednicarbate (20). In a placebo-controlled, double-blind, randomised study of MPA vs. these agents (20), scarified test areas were treated without occlusion in 78 volunteers with healthy skin and with occlusion in 60 volunteers. The study showed that MPA ointment and fatty ointment were very well tolerated in scarified skin under both occlusive and non-occlusive conditions. Among the 20 volunteers given MPA cream under occlusive conditions, only one developed local irritancy. In contrast, treatment with clobetasol propionate induced significantly more pronounced atrophy and telangiectasia, whereas prednicarbate treatment was discontinued after 3 weeks because of local irritancy (20).

MPA has been compared with another fourth generation topical corticosteroid, mometasone furoate (21). The double-blind, 6-week, occlusive, randomised trial, performed in 20 healthy volunteers, showed that treatment with mometasone furoate resulted in atrophogenicity and a higher incidence and severity of telangiectasia compared with MPA (Figure 3).

In clinical trials, signs of atrophy were observed in only two of more than 1900 patients with eczematous disorders treated with MPA cream, ointment or fatty ointment (5). Because both the patients had suffered from eczema for several years and the signs of atrophy occurred within a very short period of time of the initiation of MPA treatment, it is probable that pre-existing atrophy had been unmasked by the antieczematous action of MPA (5).

Systemic Effects on Hypothalamus-Pituitary-Adrenal Axis

MPA has a minimal effect on the hypothalamus-pituitary-adrenal (HPA) axis, with clinical experience available from

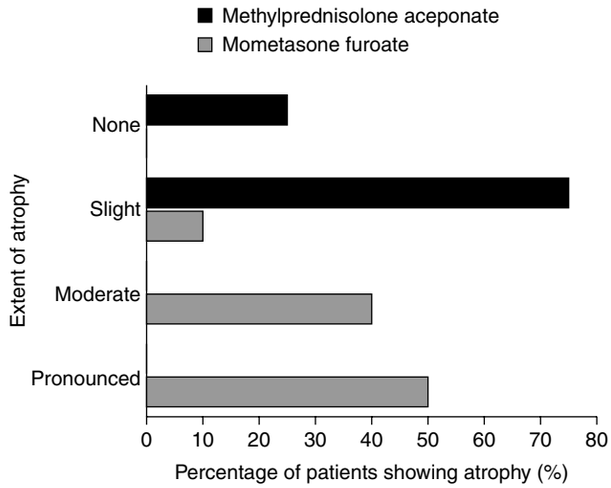

Figure 3 Percentage of patients with eczema who developed slight, moderate or pronounced atrophy following a 6-week occlusive trial with either methylprednisolone aceponate or mometasone furoate (14)

long-term use for up to 4 or 6 months (19). This is an important advantage compared with other topical corticosteroids and has important implications for long-term therapy, particularly in children, as suppressed endogenous cortisol levels may lead to adrenocortical failure and growth disorders in infants and children.

Two multicentre studies were carried out on the long-term effect on steroid-responsive chronic dermatoses. Patients received either MPA fatty ointment one to three times daily for up to 4 months (study 1) or MPA cream, ointment or fatty ointment one to three times daily for up to 6 months (study 2). In study 1, plasma cortisol levels measured in 45 patients showed no inhibition of the HPA axis, even after maximal administration of 1000 g MPA fatty ointment. In study 2 (n = 256), no systemic adverse effects, such as atrophy, telangiectasia or striae were observed. Local adverse events were mild and temporary, occurring in 7% of patients (19).

Even under extreme conditions of whole body occlusion, no fall below normal cortisol levels was observed, and circadian cortisol rhythm was maintained. In contrast to clobetasol propionate and betamethasone valerate, MPA does not lead to suppression of the HPA axis (5).

Suitability of MPA for Children and Infants

The local application of topical corticosteroids requires caution in paediatric patients because of their large surface-to-volume ratio (22). In this respect, MPA may be a suitable treatment for children, because it provides rapid and effective but gentle treatment without local and systemic side effects. Thus, in most countries, MPA cream, ointment and fatty ointment have been approved for the treatment of children of all ages for up to a period of 4 weeks. In particular, the milk emulsion formulation of MPA is very acceptable cosmetically and can be used safely and effectively in infants and young children aged 2–48 months (23).

Furthermore, MPA has been shown to have a fast onset of action (and relief) in several paediatric studies (22,24), which can be particularly important for children, who find it much more difficult not to scratch than adults (22,24).

The paediatric use of MPA has been supported by several clinical studies (22,24,25), including the use of MPA in infants less than 4 months of age (22). In double-blind comparison studies (n = 220), a successful response was achieved with MPA in over 96% of patients, with no local or systemic adverse effects reported (22). No effect was observed on plasma cortisol levels with MPA in a double-blind comparison study of MPA, prednicarbate and hydrocortisone 17-butyrate; the different treatments were applied over 7 days, using non-occlusive dressings, in 20 children with atopic dermatitis, aged between 6 months and 10 years.

MPA for Facial and Scalp Eczematous Disorders

Traditionally, the use of topical corticosteroids on the facial area has been regarded cautiously for several reasons. Besides the cosmetic aspects involved, the facial skin is particularly sensitive to corticosteroids because of greater absorption and higher density of corticosteroid receptors compared with other areas of the skin. However, the minimal risk of side effects with MPA has made it particularly suitable for application in eczematous diseases of the face.

Post-marketing surveillance has demonstrated an excellent therapeutic response to MPA in patients with facial eczematous disease, with no side effects (26). In a large, observational study of once-daily treatment with MPA cream or ointment for up to 4 weeks in 575 patients with facial eczematous disease (including 46.4% atopic dermatitis, 24.6% contact eczema, 15% seborrhoeic eczema and 1.7% photodermatoses), there were no reports of perioral dermatitis or atrophy (thinning of skin, telangiectasias) (26). The vast majority of patients and doctors (99%) graded the resulting eczema as either 'distinctly improved' or 'asymptomatic' following the use of MPA cream or ointment (Table 1). At the end of therapy, the medical assessment of individual patients showed that 66.3% of patients were 'asymptomatic', whereas a 'distinct improvement' was observed in 32.9% of patients, a 'moderate effect' in 0.6% of patients and no effect in only 0.2% of patients. The onset of action of MPA was stated by 91% of patients and 87.3% of doctors to occur by day 5 of treatment.

Good tolerability results with excellent efficacy were also demonstrated in another, large, observation study of 1744 patients who had atopic eczema of the scalp, psoriasis, seborrhoeic eczema and other non-specific scalp conditions.

Table 1 The course of individual symptoms with methylprednisolone aceponate treatment (cream or ointment) in eczematous disorders of the face as rated by the physician at the beginning and end of therapy (adapted from Ruzicka & Zaumseil [26])

	Severe symptoms (%)		*Moderate symptoms (%)*		*Mild symptoms (%)*		*Absent symptoms (%)*	
Type of symptom	*Start of therapy*	*End of therapy*	*Start of therapy*	*End of therapy*	*Start of therapy*	*End of therapy*	*Start of therapy*	*End of therapy*
Erythema	52.8	–	41.5	–	–	34.9	–	63.5
Infiltration	11.4	–	39.4	–	35.5	14.3	–	84.7
Weeping/crusts	5.0	–	16.6	0.4	25.0	2.3	53.4	97.3
Scaling	11.8	–	38.0	0.2	34.9	12.7	–	87.1
Itching	46.9	–	32.7	1.2	15.6	14.5	4.8	84.4
Burning	13.7	–	29.5	0.6	27.9	3.3	28.9	96.1

Almost all (98%) patients and physicians rated the tolerability of the MPA solution as good or very good. Only 1.4% of patients reported side effects, which were mainly mild, and included a local burning sensation (27).

MPA for Treatment of Sunburn

Despite the absence of controlled clinical trials supporting treatment, topical corticosteroids, usually as milk preparations, have often been used to treat acute sunburn. In a randomised, controlled, intraindividual comparison study, MPA milk was found to be as effective as 0.1% hydrocortisone butyrate emulsion in the treatment of simulated sunburn in 24 healthy volunteers. Within 4–5 days of treatment, areas of simulated sunburn treated with MPA milk showed significant clinical improvement compared with non-treated areas (28).

MPA in the Treatment of Psoriasis

Psoriasis is a common skin disease, affecting approximately 1–2% of the general population in the USA and UK (29). The choice of therapy is determined by the manifestation of psoriasis, extent of lesions and subjective discomfort (29–31). Preliminary results suggest that MPA may achieve good clinical results in various forms of chronic therapy-resistant psoriasis, including both progressive and stationary phases (32,33), whereas in terms of its antipsoriatic activity and tolerability, MPA is comparable to calcipotriol, a topical vitamin D analogue (34). An excellent therapeutic effect was observed in an observational study (n = 1744) of MPA in patients with scalp psoriasis, atopic eczema of the scalp, seborrhoeic eczema and other non-specific scalp conditions (27). The tolerability of MPA was rated as good or very good.

DISCUSSION

As one of the first-in-class, fourth-generation, topical corticosteroids, MPA has been designed to provide an optimal balance between efficacy and tolerability. This has been reflected by the excellent therapeutic index rating awarded to MPA by the German Society of Dermatology, who have recently published a therapeutic index for the topical corticosteroids most widely used in Germany, comparing their efficacy and adverse effects (Table 2) (35).

As a first-line choice for the topical treatment of eczematous disorders, MPA has many advantages. MPA provides rapid, reliable and highly effective treatment for eczematous disorders, including paediatric disease and facial and scalp eczema, and has excellent local and systemic tolerability. MPA effectively treats sunburn and has shown promising results in the treatment of psoriasis. The wide range of formulations (0.1%) of MPA, including cream, ointment, fatty ointment, milk emulsion and alcohol solution, enables treatment to be tailored to the individual patient (Table 3).

Table 2 Methylprednisolone aceponate has an excellent benefit-to-risk ratio as assessed by the Therapeutic Index (TIX), recently published by the German Society of Dermatology (DDG) [35]

Topical corticosteroid	*Efficacy score**	*Toxicity score†*	*TIX rating‡*
Methylprednisolone aceponate	18.0	9.0	2.0
Mometasone furoate	18.0	9.0	2.0
Prednicarbate	18.0	9.0	2.0
Clobetasol propionate	27.0	17.0	1.5
Hydrocortisone butyrate	14.0	10.0	1.4
Betamethasone valerate	18.0	15.0	1.2

*Criteria used by the DDG for assessing efficacy included studies on vasoconstriction and efficacy in inflammatory skin disorders, such as atopic dermatitis. †Criteria used to assess side effects included skin atrophy, action on hypothalamus-pituitary-adrenal axis and allergenic potential. ‡Based on the ratio of efficacy to side effects, the more effective a corticosteroid and the lower its side effects, the higher its TIX rating.

Table 3 Labelling of methylprednisolone aceponate (MPA) compared with that of topical immunomodulators tacrolimus and pimecrolimus

	MPA	*Tacrolimus/pimecrolimus*
Indication	Atopic dermatitis, contact eczema, degenerative eczema, dyshidrotic eczema, vulgar eczema, eczema in children First-line therapy	Tacrolimus: moderate to severe atopic dermatitis Pimecrolimus: mild to moderate atopic dermatitis Non-responders or those intolerant to conventional therapy Second-line therapy
Formulations	Milk, cream, ointment, fatty ointment, solution	Tacrolimus: ointment Pimecrolimus: cream
Dosage	Once daily	Twice daily
Use in infants and children	No restrictions in most countries for cream, ointment and fatty ointment Milk formulation – age:4 months	Age:2 years
Treatment scheme and duration of use	MPA cream, ointment or fatty ointment: 12 weeks in adults; 4 weeks in children MPA solution: 4 weeks MPA milk: 2 weeks	Short-term or long-term intermittent
Pregnancy/breast feeding	Not during first trimester of pregnancy Nursing mothers should not apply to the breast	Tacrolimus: not during pregnancy/breast feeding Pimecrolimus: during pregnancy only if physician deems it necessary. Not during breast-feeding
Further restrictions	None	Minimise sun exposure during first treatment No occlusive treatment

In addition, the once-daily administration of MPA promotes patient compliance while maintaining efficacy comparable to that of most reference topical corticosteroids that are applied twice daily. Moreover, its rapid efficacy and lack of undesirable local and/or systemic side effects make MPA particularly suitable for use in children and infants because of their requirements for rapid relief and large surface-to-volume ratio (22).

Extensive clinical experience, proven efficacy and a favourable tolerability profile have helped to maintain MPA as a first-line treatment for eczema. Compared with the recently introduced topical immunomodulators (TIMs), MPA is licensed for use in a broader range of indications and is available in a greater number of formulations. MPA can be used in young infants, including those below 2 years of age, whereas TIMs are presently registered for use only in patients over 2 years of age.

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