REVIEW ARTICLE

Current topical and systemic approaches to treatment of rosacea

HC Korting,* C Schöllmann

Department of Dermatology and Allergology, Ludwig-Maximilians-Universität, Munich, Germany
*Correspondence: HC Korting. E-mail: h.c.korting@lrz.uni-muenchen.de

Abstract

Rosacea is a common, often overlooked, chronic facial dermatosis characterized by intermittent periods of exacerbation and remission. Clinical subtypes and grading of the disease have been defined in the literature. On the basis of a genetic predisposition, there are several intrinsic and extrinsic factors possibly correlating with the phenotypic expression of the disease. Although rosacea cannot be cured, there are several recommended treatment strategies appropriate to control the corresponding symptoms/signs. In addition to adequate skin care, these include topical and systemic medications particularly suitable for the papulopustular subtype of rosacea with moderate to severe intensity. The most commonly used and most established therapeutic regimens are topical metronidazole and topical azelaic acid as well as oral doxycycline. Conventionally, 100–200 mg per day have been used. Today also a controlled release formulation is available, delivering 40 mg per day using non-antibiotic, anti-inflammatory activities of the drug. Anti-inflammatory dose doxycycline in particular allows for a safe and effective short- and long-term therapy of rosacea. Topical metronidazole and topical azelaic acid also appear to be safe and effective for short-term use. There are indications that a combined therapy of anti-inflammatory dose doxycycline and topical metronidazole could possibly have synergy effects. Further interesting therapy options for the short- and long-term therapy of rosacea could be low-dose minocycline and isotretinoin; however, too little data are available with regard to the effectiveness, safety, optimal dosage and appropriate length of treatment for these medications to draw final conclusions.

Received: 21 December 2007; Accepted 9 December 2008

Keywords

azelaic acid, doxycycline, metronidazole, rosacea

Conflicts of interest

None declared.

Introduction

Rosacea is a common, but often overlooked, chronic cutaneous disease of uncertain aetiology with many different clinical manifestations.[1] The dermatological condition primarily affects the centre of the face, especially the cheeks, nose, chin and central forehead. Furthermore, ocular manifestations may be present, possibly occurring more frequently than previously presumed.[2] The earliest and not rarely predominant complaints linked to rosacea are intermittent, central facial flushing and erythema. Many patients complain of a stinging pain associated with episodes of flushing while itching is nearly always absent. Flushing episodes can occur unpredictably or can be linked to environmental, chemical, food or emotional triggers (i.e. exposure to sun, cold weather, hot beverages, sudden emotion like laughter or embarrassment and alcohol consumption).[1] The progression of rosacea is variable; however, typical stages are represented by papules and pustules and, finally, rhinophyma.

Epidemiology

Conventional wisdom has it that rosacea is more common in women,[3] while the clinical manifestations of the disease are more severe in men.[4] By contrast, a recent analysis based on a cross-sectional study of rosacea (1995–2002) on 50 235 outpatients shows that overall, both sexes were equally affected by the disease.[5] Epidemiological data at large suggest that there is a genetic predisposition for this disease, with several intrinsic and extrinsic factors potentially correlating with the phenotypic expression of rosacea.[6]

Rosacea most frequently occurs in the light-skinned Caucasian population, and in persons between 30 and 50 years.[1,3,7] Estimates of the prevalence of rosacea range from less than 1% to 10%.[4,5,8] A recent investigation suggests that the prevalence of rosacea has been substantially underestimated. Among 850 females aged up to 70 years recruited from the general population in London and Los Angeles, 174 (20.5%) were identified as having rosacea, with

rosacea prevalence decreasing with the degree of skin colour.[9] In contrast, data collected by the Rochester Epidemiology Project indicate a rosacea prevalence of 2.1% among adults, suggesting that the actual occurrence of the disease is rarer than previously reported.

Pathophysiology

There is a lack of understanding with regard to the pathogenesis of rosacea. The important issue of whether or not the papules are based in the follicle is still unclear at this time.[10] It is also unknown if accumulated sun damage might be involved in the pathogenesis, and, furthermore, whether neurological and hormonal mechanisms are involved in flushing reaction and phyma formation and, if so, which ones (for review, see Baldwin[10]). What is known is that the pathophysiology of rosacea likely is inflammatory, and that most interventions appear to modulate the inflammatory process.[11,12] Moreover, there is a growing consensus that bacterial infection most likely is not involved in rosacea pathogenesis.[10] Because of the poor understanding of the pathogenesis of rosacea, treatment has generally targeted the symptoms/signs rather than the potential underlying causes of the disease. Despite the incomplete understanding of the pathogenesis of rosacea, therapeutic options continue to expand (for review, see Pelle *et al.*[13]).

Classification and staging

A standard classification system for rosacea was published in April 2002.[14] Developed by the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea and reviewed by rosacea experts worldwide, it describes primary and secondary features of the disease. Primary features were identified as flushing (transient erythema), nontransient erythema, papules and pustules and telangiectasia. Secondary features were identified as burning or stinging, presence of plaques, dry appearance, presence of oedema, peripheral location (extrafacial signs and symptoms) and phymatous changes.[14] Finally, the committee recognized four patterns of signs and symptoms, designated as subtypes.

Subtype 1 (erythematotelangiectatic rosacea) is characterized by flushing and persistent central facial erythema with telangiectases common but not essential. Subtype 2 (papulopustular rosacea) includes persistent central facial erythema with transient papules, pustules, or both in a central facial distribution. Burning and stinging may also occur. Subtype 3 (phymatous rosacea) may include thickening of the skin, irregular surface nodularity, and enlargement (e.g. as rhinophyma). Patulous, expressive follicles may appear in the phymatous area, and telangiectases may be present as well. Subtype 4 (ocular rosacea) may be characterized by a watery or bloodshot appearance, foreign-body sensation, burning or stinging, dryness, itching, light sensitivity, blurred vision and telangiectasia of the conjunctiva and lid margin; lid and periocular erythema, blepharitis, conjunctivitis and irregularity of the eyelid may also be present. Using the National Rosacea Society Expert Committee's standard classification system, among 177 women with rosacea recruited from the general population in London and Los Angeles recently (as cited above[14]), 161 (92.6%) were considered to have subtype 1 while only 13 (7.4%) had the papulopustular subtype 2. Fourteen women (8%) had ocular involvement and seven (4%) rhinophyma.[9]

To enhance the utility of the classification system, the Committee devised a standard method for assessing different grades of severity.[15] As indicated in the proposals of the Committee, primary signs may be graded as absent, mild, moderate or severe (0–3), and most secondary features may be graded simply as absent or present.[15] According to the researchers, such a standard grading system in combination with a standard classification system is often useful and essential in analysing results from different sources and performing research. In turn, standard parameters and terminology may provide a common reference for the diagnosis, treatment and estimation of results in clinical practice. The recent study among 177 women with rosacea already addressed above suggests that mild disease is more common in females with subtype 1, affecting almost 75% of those individuals, while the skin disease severity was graded as moderate in 19% of the women with subtype 1 and severe in 9%.[9]

Classification of the polymorphic disease rosacea into four subtypes is also controversial among some researchers. For example, Albert M. Kligman believes that reducing the disease to four main types is a vast oversimplification and does little to clarify the complexities of this entity.[4] For Kligman and other researchers, rosacea fundamentally is a vascular disorder beginning with episodes of flushing and histopathologically showing classic signs of damage to the dermal matrix; namely, elastosis, collagenolysis and increased glycaminoglycans.[4]

Therapy of rosacea

Therapy based on rosacea subtypes

Although rosacea is a disease that causes high psychological strain in those affected, it has no adverse effect on vital functions. For this reason, preference should be made for medications with an especially favourable risk profile.

The four subtypes differ greatly with regard to their response to various therapy strategies. The erythematotelangiectatic subtype is the most difficult to treat. Most patients respond poorly to topical or oral medications. There are some data indicating that isotretinoin transiently may improve erythema resulting from inflammation, while medications that antagonize flushing may be helpful for other patients.[10] Vascular laser and light therapy have been increasingly utilized for control of the generalized erythema, flushing, and telangiectasia characteristic for this subtype of rosacea.[16,17] Mild forms of ocular rosacea respond readily to topical medications and eyelid hygiene; more severe forms substantially respond to oral antibiotics, with tetracyclines being used most often.[10] There is a limit to the use of topical and/or oral medications

in the treatment of phymatous rosacea. Often surgery or laser ablation is necessary to eradicate very pronounced lesions.[10] Isotretinoin, in particular, has been shown to have the potential to delay the progression of rhinophyma (Irvine *et al.*, as cited in Baldwin[10]) and to be an option for patients with treatment-resistant rosacea.[18] The papulopustular subtype of rosacea is the easiest type to treat. A lot of patients respond well to topical medications such as metronidazole, azelaic acid, benzoyl peroxide, clindamycin, and erythromycin.[10] Sometimes, however, topical medications reach the limitations of their effectiveness. At this point at the latest, a systemic therapy is necessary. Since 2006, topical medications are no longer being applied as a first-line therapy in the USA in all cases. With the advent of a once-daily, non-antibiotic dosing of doxycycline as a therapy option, the systemic approach is being used more often as a first choice medication.[6] In addition, recent studies suggest that a combined therapy (e.g. once-daily, anti-inflammatory doxycycline combined with topical metronidazole) might possibly further increase effectiveness[19,20].

The therapy options discussed in detail in the following primarily address the problems of patients with the moderate to severe papulopustular subtype.

Topical medications

Three topical medications have been approved by the US Food and Drug Administration (FDA) for rosacea, and all three, including 0.75% and 1% metronidazole, 10% sodium with 5% sulphur, and 15% azelaic acid, are indicated for the management of papules, pustules and erythema.[13] Moreover, other medications are used off-label for this disease.

Metronidazole

In the 1980s, it was shown for the first time that topical metronidazole can be used successfully in the treatment of rosacea.[21] Today, besides azelaic acid (see below), metronidazole is considered the first choice for the topical therapy of rosacea. Twice-daily metronidazole (0.75%) was well-tolerated and effective in the treatment of 582 patients with mild to moderately severe papulopustular rosacea of various aetiologies and locations. Its mean erythema severity score decreased significantly and was reduced by nearly 50% by week 12.[22] For a long time, a twice-daily application of 0.75% gel formulation was considered to be the optimal dosage until the effectiveness of a once-daily dosage of 0.75% and 1% metronidazole formulation could be shown in a 12-week, randomized study.[23] In 2006, it was moreover shown that the type of formulation in fact might play a subordinate role with regard to effectiveness: metronidazole cream, gel and lotion have been shown to have similar efficacy, regardless of whether a concentration of 0.75% or 1% is chosen or a once-daily or twice-daily regimen.[24]

The efficacy of topical metronidazole vs. a placebo has been demonstrated in various trials; however, only nine of these were of acceptable quality. In these studies, metronidazole was found to be an effective medication with few adverse effects, whereby most of the adverse effects were mild, including pruritus, skin irritation and dry skin (see Van Zuuren *et al.*[25]). A new, stable aqueous metronidazole gel (1%) might possibly even be a better tolerated alternative with a low potential for causing sensitization reactions and no evidence for causing phototoxic or photo-allergic reactions.[26] In patient self-assessment, there was no statistical difference between topical azelaic acid and topical metronidazole, whereas a significantly higher physician rating of global approvement was achieved with azelaic acid.[27,28] However, the difference between the two medications with regard to the reduction of inflammatory lesions was too marginal to be of clinical relevance.[28] A new study shows that the efficacy of the once-daily application of metronidazole (1% gel) and twice-daily azelaic acid 15% gel was similar.[29] Both medications were well tolerated, but the number of adverse effects was lower after application of metronidazole whereby the adverse effects in both groups have been reported be mild to moderate.[28] Furthermore, topical metronidazole might be as effective as oral tetracycline,[21,30] benzoyl peroxide 5%/erythromycin 3% gel,[31] and topical permethrin (5% cream),[32] but more evidence is needed.

Sodium sulphacetamide and sulphur

For more than 50 years, sodium sulphacetamide 10% with sulphur 5% has provided a safe, well-tolerated and effective option for the treatment of rosacea,[13] but the quality of studies concerning this matter is generally poor. By means of an 8-week therapy, a significant reduction in inflammatory lesions (78% vs. 36%, respectively; $P < 0001$) and facial erythema (83% vs. 31%, respectively; $P < 0001$) was achieved compared to a vehicle.[33] Adverse effects (pruritus, contact dermatitis, irritation, and xerosis) occurred in 19% of users, but they were reported to be mild (Lebwohl *et al.*, as cited in Pelle *et al.*[13]). Anecdotal evidence and preliminary studies suggest at least some additional benefit when sodium sulphacetamide 10%/sulphur 5% is applied in combination with topical metronidazole.[34] Moreover, newer 'wash-on-wash-off' sodium sulphacetamide formulations have further additional benefits such as less lingering odour, lower irritation potential and fewer interactions with other topical regimens or cosmetics (Arndt and Bowers, as cited in Pelle *et al.*[13]). Generally, there is insufficient evidence concerning the effectiveness of sulphacetamide with sulphur in the treatment of rosacea.

Azelaic acid

Azelaic acid, mostly applied as 15% gel or 20% cream, is a naturally occurring saturated dicarboxylic acid[35] approved for the treatment of mild to moderate rosacea in various countries. Its effectiveness and safety has been demonstrated in two phase-III, vehicle-controlled, randomized trials in 664 patients with papulopustular rosacea. In these studies, improvement of erythema

was found in 44% and 46% of rosacea patients treated with azelaic acid vs. 29% and 28% of patients treated with a vehicle.[36] Analysis of the reduction of inflammatory papules and pustules led to comparable results.[37]

Benzoyl peroxide, erythromycin and clindamycin

Benzoyl peroxide, erythromycin and clindamycin are sometimes used off-label in the treatment of rosacea although there are not many studies available covering these three medications.

Tacrolimus

Topical tacrolimus (0.1 or 0.075% % ointment) is a macrolide non-steroidal immunomodulatory preparation approved in the USA that acts by inhibiting T-cell activation and cytokine release.[38] It is approved so far for the treatment of atopic dermatitis only but has also been reported to be an effective treatment for steroid-induced rosacea,[39,40] yet there are not many studies available in this regard. It has been claimed that tacrolimus twice daily combined with 100 mg of minocycline (twice daily) clears most patients with steroid-induced rosacea within 1–2 months.[13]

Tretinoin

In a few small series, topical retinoids like tretinoin have demonstrated benefit for rosacea, although the clinical response is delayed and often not evident until 2 or more months after initiation of therapy.[41–43] The use of topical retinoids in rosacea has often been avoided because of the possible angiogenesis supporting effects of this substance group, yet so far a visible increase in cutaneous vascularity or the development of telangiectasia has not been observed.[41,43] In contrast, a lessening of erythema and a partial to complete disappearance of telangiectasia has been reported in patients treated with 0.025% tretinoin cream.[41] However, on the whole, the trial situation for this medication is relatively poor.

Oral medications

Oral antibiotics have been used off-label for the treatment of rosacea for more than 50 years, and tetracyclines have been the drug class most often used. Antibiotics were used to treat rosacea based on the presumption (and from today's view a presumption that is most likely wrong) that bacterial pathogens are, in part, responsible for the development of the disease.[10]

Tetracyclines

Tetracyclines are broad-spectrum antibiotics that have been used in rosacea treatment for decades although never approved by the FDA for this indication.[13] They were first widely prescribed by dermatologists in the 1950s when it was discovered that they were effective in the treatment of acne. Tetracycline has also been reported to be effective in the treatment of papulopustular rosacea, in which context a 3- or 4-week treatment regimen was required to achieve substantial improvement.[44] Tetracycline

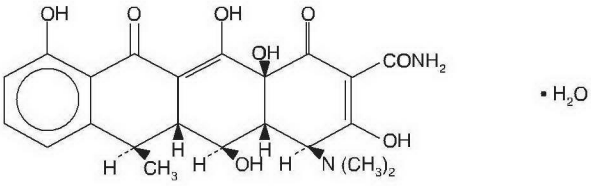

Figure 1 Chemical structure of doxycycline.

(250–1000 mg per day), doxycycline (100–200 mg per day, and lately also 20–40 mg per day) and minocycline (100–200 mg per day) are the most commonly used compounds.[10] Tetracyclines are contraindicated in pregnant women. Until recently, the use of oral tetracyclines for rosacea was based primarily on clinical experience and a limited number of placebo-controlled studies.[13,45,46] Only the most recent studies were conducted on the basis of a sufficiently large number of patients reflecting their generally high quality,[6] but nevertheless further randomized, controlled studies are needed.

Today researchers for the most part agree that it is mainly the non-antibiotic properties of the various tetracyclines that are responsible for the effectiveness of these substances in skin diseases such as rosacea. In fact, it is the non-antibiotic actions of tetracyclines such as the inhibition of angiogenesis, the inhibition of neutrophil chemotaxis, the inhibition of pro-inflammatory cytokines and the inhibition of matrix metalloproteinases that significantly contribute to the clinical effectiveness for various indications – in addition to rosacea also being used for bullous dermatoses, neutrophil diseases, periodontitis and autoimmune disorders such as rheumatoid arthritis and scleroderma, pyoderma gangrenosum, sarcoidosis, aortic aneurysms, and cancer.[47] In particular, the ability of tetracyclines to reduce the inflammatory response is believed to be the rationale for its effectiveness in treating rosacea (Greewald *et al.*, as cited in Baldwin[10]).

Besides the classic drug, tetracycline itself, today second generation tetracyclines, including minocycline and especially doxycycline (Fig. 1), are being successfully used in the treatment of rosacea. In comparison with their parent drug, these tetracyclines can offer advantages to the dermatologist over tetracycline. For example, they have an improved bioavailability, a longer elimination half life, and they can be taken with food which minimizes gastrointestinal side effects.[48] A big advantage of these substances, moreover, is represented by the fact that they are helpful for rosacea patients already at a sub-antimicrobial (also at a time anti-inflammatory) dose.[6] Thus, an effective and tolerable long-term therapy is possible without having to accept the disadvantages of a long-term antibiosis, i.e. undesired side effects such as candidal vulvovaginitis or gastrointestinal distress, and – of worldwide importance – the propagation of bacterial resistance.[49] As bacterial resistance is a

global problem, the use of non-antibiotic alternatives such as low-dose doxycycline should be preferred in the treatment of rosacea where there is no established evidence of a microbial pathogenesis.[10]

Anti-inflammatory dose doxycycline is the only tetracycline approved in the USA for long-term use for up to 12 months.[10] The used dosage of 20 mg doxycycline hyclate twice daily or 40 mg once daily has been shown to effectively treat papulopustular rosacea with an especially favourable risk–benefit ratio. The first oral medication approved by the FDA for the treatment of rosacea in the USA is marketed as Oracea™. Oracea™ is a 40-mg capsule of doxycycline monohydrate containing 30 mg immediate-release and 10 mg delayed-release doxycycline beads. In contrast to other oral therapies, anti-inflammatory dose doxycycline is taken once daily, which may increase treatment compliance.[49] Furthermore, it has been shown that a 40-mg controlled release formulation of doxycycline conferred peak anti-inflammatory efficacy in the treatment of rosacea.[50] At sub-antimicrobial doses, long-term use of anti-inflammatory dose doxycycline might not exert selective pressure on micro-organisms, and thus not lead to the development of antibiotic-resistant organisms[10,49,51]. Recently, two phase III, parallel-group, multicentre, randomized, double-blind, placebo-controlled studies have demonstrated the efficacy and safety of a 16-week treatment with anti-inflammatory doxycycline (40 mg) administered once daily in patients with rosacea.[6] Both studies included patients with a marked number of inflammatory lesions (10–40 papules, < 2 nodules), moderate to severe erythema and the presence of telangiectasia. Patients received 40 mg of controlled-release doxycycline ($n = 269$) or placebo ($n = 268$) for 16 weeks. The primary endpoint was the mean change from baseline in inflammatory lesion count. At week 16, the mean change from baseline in lesion count in the doxycycline groups was −11.8 in one study and −9.5 in the other study compared with −5.9 and −4.3, respectively, in the placebo groups ($P < 0.001$ for both comparisons, Figs 2 and 3). The active medication was well tolerated with nasopharyngitis (4.8%), diarrhoea (4.4%) and headaches (4.4%) constituting the most common adverse effects being found only marginally more frequently than in the control group, if at all.[6] Thus, today anti-inflammatory doxycycline (40 mg) administered once daily must be considered to be – besides topical therapies with metronidazole or azelaic acid – a promising therapy strategy for rosacea of papulopustular subtype.

Current research on comparably small patient numbers suggests that a combined therapy of anti-inflammatory dose doxycycline and topical metronidazole (0.75% topical lotion or 1% topical gel) leads to an especially effective alleviation of inflammatory lesions. The therapeutic effect might be greater and set in faster than with metronidazole alone[19] (Fowler, 2007, poster presented at: American Academy of Dermatology 65th Annual Meeting; February 2–6, 2007; Washington, DC). Yet reliable data are not available as to whether the effectiveness of the combination is better than that of anti-inflammatory dose doxycycline alone.

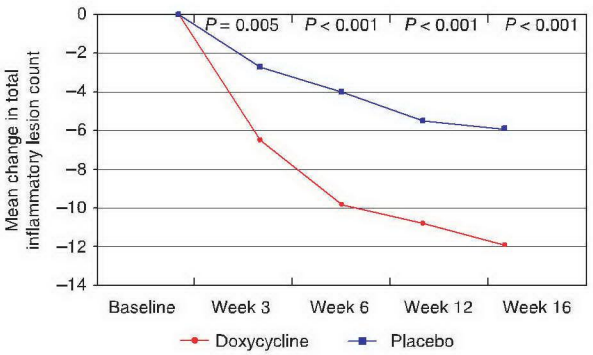

Figure 2 Mean change from baseline in total inflammatory lesion count (papules + pustules + nodules) through week 16 in study 301 (from Del Rosso *et al.*[6] with permission).

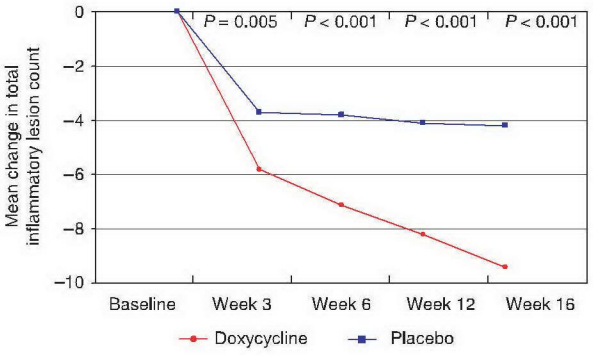

Figure 3 Mean change from baseline in total inflammatory lesion count (papules + pustules + nodules) through week 16 in study 302 (From Del Rosso *et al.*[6] with permission).

Macrolides

Although oral erythromycin at a dose of 250–1000 mg per day is considered an effective drug for the treatment of papulopustular rosacea, it is not often used because of the gastrointestinal side effects it frequently causes.[10] As a general rule, the use of erythromycin is reserved for those patients that are intolerant, allergic or refractory to tetracyclines or in cases where tetracyclines are contraindicated, such as in pregnancy.[13]

As second-generation macrolides, clarithromycin and azithromycin take effect faster and are better tolerated with regard to gastrointestinal side effects than orally administered tetracyclines, metronidazole and ketoconazole.[52] In several smaller studies, both have been found to be effective and tolerable drugs in the short-term therapy of rosacea.[52–54] After a 12-week treatment with azithromycin in decreasing doses, there was a 75% decrease in total scores and an 89% decrease in inflammatory lesion scores

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.